A.M.A.
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JANUARY 1955
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A. M. A.
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AMERICAN MEDICAL ASSOCIATION

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FUNDAMENTALS OF NEUROPATHOLOGY

By

WILLIAM BROOKS DUBLIN, M.D.
Chief, Laboratory Service
Veterans Administration Hospital
Associate Professor of Pathology
University of Colorado School of Medicine
Consultant in Neuropathology
Denver General Hospital

This is a text of pathology **dealing with those diseases having nervous system manifestations.** The general plan of approach is on a basis of succinct general pathology with adequately extended consideration of nervous system; the more essential general clinical and pathologic data are presented for orientation, leading up to the neuropathologic discussions.

In the main, the basis of classification and organization of material is the nature of the pathologic process, rather than the syndrome or grouping of clinical symptoms; however, **clinicopathologic correlation** is constantly borne in mind. Where indicated, biochemical and physiologic data are applied.

Those histologic methods are emphasized which are comparatively **simple and relatively likely to find use in the general pathology laboratory,** and which are truly essential to the adequate routine study of neuropathologic material. In the presentation of technical procedure, the in-between-the-lines problems are discussed, so that the person applying the method will have a minimum of the grievance of trial and error.

The illustrations are high in practical teaching value and in technical quality, and coverage is unusually complete.

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Editorials

LETTER FROM THE EDITORS

WE HOPE that you will like the "new look" of the ARCHIVES. The cover has been completely redesigned, and illustrations and space have been rearranged to present a maximum amount of material in the minimum compass compatible with good readability. If you disapprove, the editors accept a full share of responsibility for these changes, because they were consulted freely during the planning. The editors were somewhat disturbed by the fact that this is the second change in the format of the ARCHIVES since its publication began, in 1919. However, they were glad to accede to the new proposals for the cover provided it contained at least a partial list of the table of contents, a suggestion which was readily accepted by the business management.

It has been felt, in line with the policy of the Editorial Board to attempt to keep abreast of the major interests of all neurologists and psychiatrists by such innovations as the Scientific Exhibits, editorials on timely topics, etc., some change in the physical form of the ARCHIVES was in order. The Editorial Board agrees and feels that the changes made are well conceived and executed. The editors will strive to continue to do their part in selecting new, reliable, and informative material for the readers and in presenting it without undue delay.

CHIEF EDITOR

STUDIES ON BLOOD-BRAIN BARRIER WITH RADIOACTIVE PHOSPHORUS

V. Effect of Cerebral Injuries and Infarction on the Barrier

LOUIS BAKAY, M.D., Boston

PREVIOUS investigations revealed the existence of a physiological barrier which prevents the central nervous system from incorporating a large percentage of the P^{32} made available to the organism by intravenous administration. Data are now accessible [1] which cover the P^{32} uptake from the blood by different parts of the normal mammalian brain at various intervals after the injection of the tracer. The exact mechanism of this process and the structure of the barrier are not known as yet, and hypotheses have to be relied upon. However, data collected under normal circumstances in the past years represent a solid enough basis on which the evaluation of changes in the blood-brain barrier, under pathological conditions, can be attempted.

Practical utilization of the blood-brain barrier concept, with the barrier investigated by radioactive isotopes and, to a less extent, by vital dyes, is carried out successfully in the diagnosis and localization of brain tumors. It has become a routine procedure in many neurosurgical centers. It has not been used to any extent to study the pathological physiology and metabolic disturbances in cerebrovascular accidents and degenerative diseases of the central nervous system, although I believe that it would be eminently suitable to give new information on chronic disorders of little-known etiology.

Unfortunately, the complex character of brain tumors made the evaluation of isotope data difficult and led to confusing interpretations regarding the nature of the physiological processes involved. It has been clearly established that those isotopes which have been successfully used to localize brain tumors (P^{32}, K^{42}, Cu^{64}, As^{76}, As^{74}, and I^{131}) concentrate, to a significantly greater extent, more in the tumor than in the surrounding brain tissue and thus a tumor-normal brain ratio exists which can be measured and usefully exploited. There are two theories to explain the high concentration of the isotope in the tumor. One explanation stresses the importance of a vigorous metabolism by the more embryonic tumor tissue, while the other lays emphasis on the local breakdown of the blood-brain barrier. Quotations from recent papers by eminent authors illustrate the point:

> The term "blood-brain barrier" can be misleading in so far as it suggests that there is some unique property of the capillary endothelium in the brain: it is the chemical nature of the brain tissue in which the capillary lies that determines what shall go through the vessel wall. Certainly the isotope is concentrated in abnormally large amounts in cerebral tumor and in inflammatory lesion, but this is a property not confined to such conditions in the brain alone [Morley and Jefferson [19]].

> The selective deposition of the radioactive dye within tumor tissue appears to depend upon the state of capillary endothelium, and concentration of the dye is directly proportional to the angioarchitectural histopathological patterns. We believe that it is the endothelium of the terminal capillaries which is of major importance [Davis and Goldstein [7]].

In order to study the changes of the blood-brain barrier in simple pathological processes, I made various artificial lesions in animals and studied their effect on the P^{32} uptake of the brain.

MATERIAL AND METHODS

The experiments were performed on cats. A small trephine opening was made over one cerebral hemisphere, with the animals under ether anesthesia. The dura was pierced with a large needle, and through this opening a stab wound was produced with a heated needle. An attempt was made to per-

From the Department of Neurosurgery, Massachusetts General Hospital.

This work was supported by a research grant (B 212-C2) from the National Institute of Neurological Diseases and Blindness, National Institutes of Health, U. S. Public Health Service.

form the lesions in a uniform fashion, and the variation in the extent of the wound was slight. The stabs were directed toward the center of the hemisphere and extended through the cortex into the white matter to a depth of 5 to 13 mm. The cats recovered promptly and revealed no neurological symptoms. A standard dose of 1 mc. of P^{32} was

Space-taking lesions were produced in another group of cats by injecting 1 to 3 cc. of melted paraffin into the depth of one hemisphere. This paraffin solidified within a few seconds and exerted considerable pressure on the surrounding brain. In most of the animals this resulted in hemiparesis of varying severity and duration. These cats were killed one

TABLE 1.—*P^{32} Content of Various Parts of Central Nervous System*

	Time Elapsed After Injury *				
	4 Hr.	6 Hr.	2 Days	14 Days	42 Days
Plasma †	10.0	10.0	10.0	10.0	10.0
Cerebral cortex					
1 mm. from surface	4.0	4.5	4.0	5.0	3.8
2 mm. from surface	1.8	1.6	2.0	2.0	2.2
3 mm. from surface	1.0	0.8	0.7	1.1	0.6
Deep white matter	0.4	0.4	0.4	0.5	0.4
Ventricular wall	5.0	6.5	7.0	6.2	5.0
Lesion	28.0	31.0	20.0	12.0	7.0
Lesion-cortex (1 mm.) ratio	7.0	6.9	5.0	2.4	1.8
Lesion-white matter ratio	70.0	77.4	50.0	24.0	17.5

* The isotope was injected two hours before death.
† Values are expressed in counts per minute per milligram of tissue and computed to a standard P^{32} plasma level.

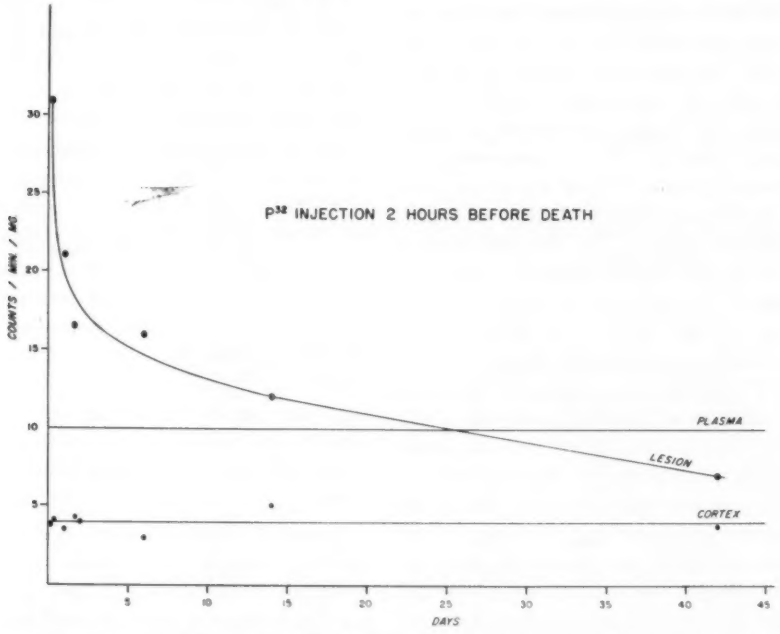


Fig. 1.—P^{32} concentration in the injured area of the brain as recorded at various intervals following the operation. Values are computed to a standard P^{32} plasma level.

given intravenously in one group of cats two hours before death. They were killed 4, 6, 24, 43, and 48 hours and 6, 14, and 42 days after the injury. In another series, the cats had the same dose of P^{32} administered intraperitoneally 10 minutes after the injury. The animals of this group were killed 47 minutes, 4 and 43 hours, and 5½ and 9 days after the operation.

hour and one, two, and eight days after the operation, which was followed by an injection of P^{32}.

After death, blood samples were taken and the brain was removed immediately and frozen. Radioautographs of cross sections of the brains were prepared on Kodak No-Screen x-ray film. After the autographs had been developed, various areas of the lesion and normal brain were isolated in the

still frozen specimens, and their radioactivity was determined by scalers. The data were computed in counts per minute per milligram of fresh tissue.

RESULTS OF EXPERIMENTS

The use of P^{32} in these experiments confronted me with a new problem, which had not occurred in the course of vital dye studies. When vital dyes entered the area of cerebral injury from the blood stream, they represented a sharp contrast to the unstained normal brain. Radioactive phosphate, on the other hand, became deposited simultaneously in both the injured and the normal brain tissue, although at different rates of concentration. In other words, the changes in P^{32} concentration in the damaged area were superimposed on the changing background of the incorporation of this same isotope by the normal cerebral tissue.

In one series of experiments, hot stab injuries were performed in the cerebral hemisphere and the cats were killed at various intervals after the operation. Two hours before death, the animals received a single intravenous dose of P^{32}. Consequently, in this series the permeability of the blood-brain barrier for P^{32} was tested at different stages of damage and repair. The concentration of the isotope in the injured region reached its maximum within the first few hours following injury (Table 1; Fig. 1). At this stage the necrotic area contained about 7 times as much P^{32} as the surface areas of the brain (superficial layer of cortex; ventricular wall) and more than 70 times as much as the depth of the cerebral hemisphere. As time elapsed and barrier permeability lessened, owing to wound repair and scarring, concentration of P^{32} in the damaged area decreased steadily. The ratio between the isotope contents of the lesion and cortex was 4:1 to 5:1 on the second day, 3:1 at the second week, and less than 2:1 at the sixth week. The isotope ratio between the lesion and the deep white matter of the normal brain diminished from a maximal 77:1 in the sixth hour to 17:1 in the sixth week. Nevertheless, it is worth while mentioning that a significant difference in permeability still existed at the end of the sixth week.

It was just as much interest to follow the changes, with the elapse of time, in P^{32} concentration of the lesion and compare them with changes in concentration of the isotope in plasma and in various parts of the normal brain. Another series of experiments was undertaken for this purpose. Similar stab wounds were performed, and 10 minutes afterwards a single intraperitoneal injection of 1 mc. of P^{32} per standard body weight was administered. The animals were killed at various intervals afterwards. Four hours after injury the lesion concentrated much more P^{32} than normal tissue, 7 times as much as the normal cortex and 70 times as much as the deep white matter (Table 2; Fig. 2). However, the cortex-lesion isotope ratio rapidly diminished and became only 2.6:1.0 at the end of the second day. From that time on the ratio decreased only slightly; it was still 1.8:1.0 on the fifth day and was 1.7:1.0 on the ninth day. Time curves of P^{32} concentration (Fig. 2) reveal the course of events. The isotope concentration in the lesion clearly followed the declining plasma curve, while, on the other hand, intact parts of the brain steadily increased their P^{32} content within the range of this experimental series.

The experiment of shortest duration was performed on a cat which received P^{32} 10 minutes after the injury and was killed 37 minutes afterwards. The P^{32} content in the center of the lesion was still only half as much as that in the plasma, but it exceeded that of the surface of the normal cortex 8 times and that of the deep white matter 90 times.

Areas of different degrees of damage were observed around the center of the stab wounds. Within the first two days following the injury the area of maximal P^{32} concentration was 8 to 10 mm. in diameter (Fig. 3). This was surrounded by a zone of 2 to 3 mm. in width, which contained 31% to 54% less P^{32} than the center. This zone showed evidence of edema but no other damage; it disappeared at the end of the second day. The region of highest P^{32} concentration also diminished in size with the lapse of time. Its diameter varied from 5 to 7 mm.

between the fifth and the ninth day. There was little change in the size of damage from the second week on, and the increase in permeability for P^{32} still covered an area of in diameter) in different depths of the hemisphere. In the surrounding area of necrosis and edema the uptake of P^{32} was high. The concentration of the isotope in the areas of

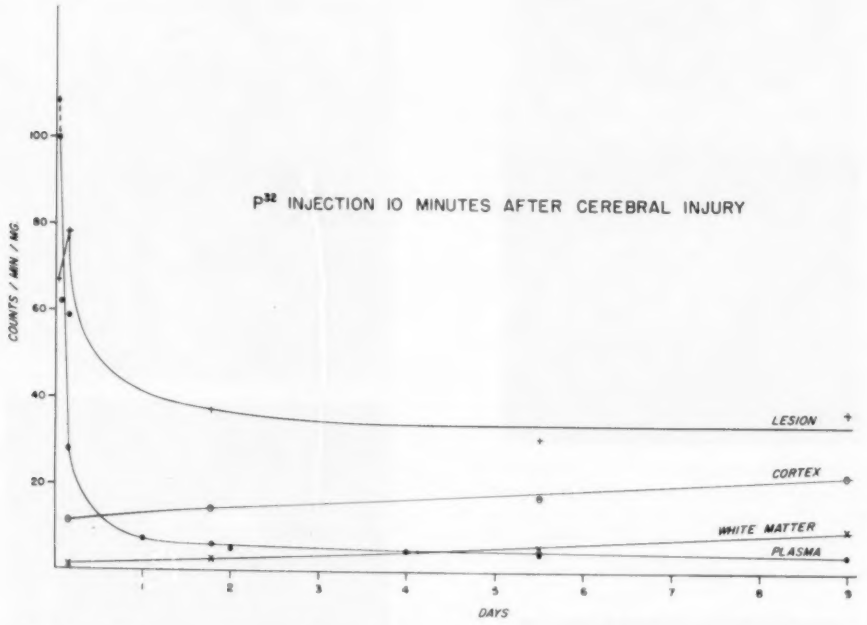


Fig. 2.—P^{32} concentration of plasma, normal brain, and cerebral lesion at various intervals after hot stab wound of the brain, which was followed immediately by the administration of the tracer.

TABLE 2.—*P^{32} Content of Various Parts of Central Nervous System*

	Time Elapsed After Injury *			
	4 Hr.	43 Hr.	5½ Days	9 Days
Plasma †	28.0	6.0	4.1	3.8
Cerebral cortex				
1 mm. from surface	11.4	14.4	17.2	22.4
2 mm. from surface	8.4	11.4	13.9	18.6
3 mm. from surface	6.2	3.9	11.5	16.7
4 mm. from surface	1.1	2.4	8.2	14.4
Deep white matter	1.1	2.4	4.9	9.8
Ventricular wall	16.8	15.0	18.4	20.8
Lesion	80.0	37.0	31.5	37.0
Lesion-cortex (1 mm.) ratio	7.0	2.6	1.8	1.7
Lesion-white matter ratio	72.0	15.4	6.4	3.8

* P^{32} (300 μc per kilogram) was injected 10 minutes after injury.
† Values are expressed in counts per minute per milligram of tissue.

4.5 by 4.0 mm. at the beginning of the seventh week (Fig. 3).

In another series of experiments space-taking lesions were produced by injecting melted paraffin into the cerebral hemisphere. The solidified material produced artificial tumors of various dimensions (4 to 10 mm. greatest damage did not differ significantly from the data obtained from the experiments with hot stab wounds. Zones of varying concentration could be distinguished at the early stages. One day after a paraffin tumor of 5 mm. in diameter was produced in the depth of the hemisphere, the surrounding necrotic

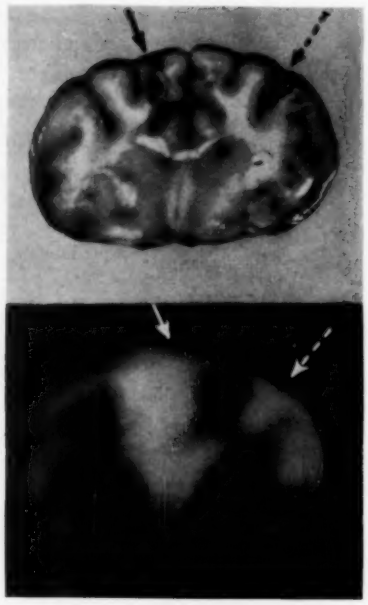


Fig. 3.—Radioautograph of cross section of a cat's brain two hours after intravenous injection of 1.2 mc. of P^{32}. Two identical hot stab wounds were made previously, the left (arrow) 4 hours and the right (dotted arrow) 42 days before death. Exposure time was 45 hours.

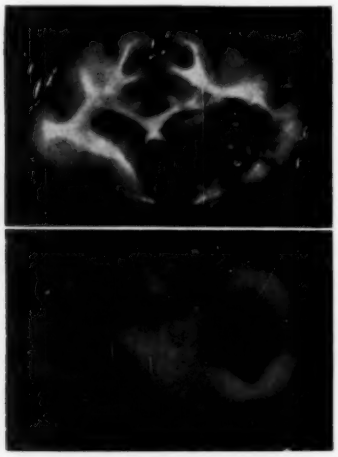


Fig. 4.—Radioautograph of transverse section of the brain. Paraffin was injected into the left hemisphere, and the cat was killed one day after the operation. P^{32} (0.6 mc.) was given at the same time. Exposure time was 67 hours.

zone of 3 to 4 mm. was found to contain great amounts of P^{32} (Fig. 4). Edema, containing 48% to 62% of the maximum activity, involved the whole ipsilateral hemisphere. Two days after a similarly placed paraffin lesion was produced, the edematous zone was restricted to 2 mm. (Fig. 5), concentrating 58% of the highest counts in the lesion. Even at this time, high counts were found in the

Fig. 5.—Radioautograph of cat's brain two days after the injection of paraffin into the right hemisphere. P^{32} (0.8 mc.) was given 24 hours before death. Exposure time was 55 hours.

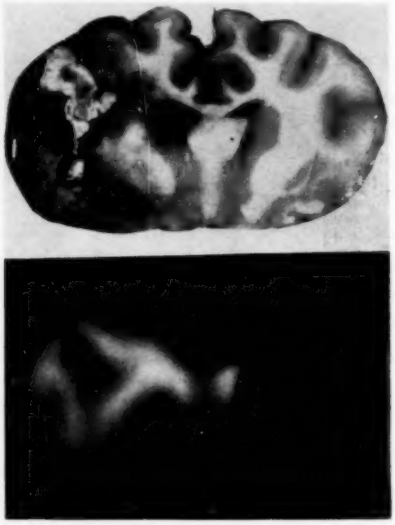
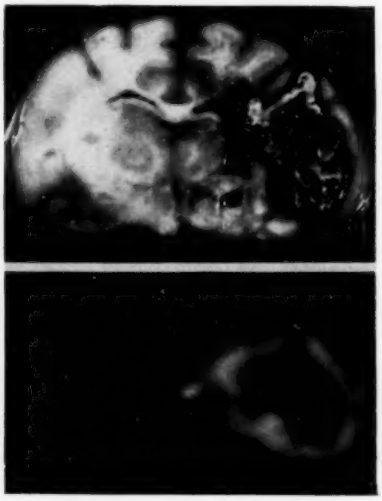


Fig. 6.—Radioautograph of cat's brain four days after the injection of paraffin into the left hemisphere. P^{32} (0.8 mc.) was administered 24 hours before death. Exposure time was 55 hours.



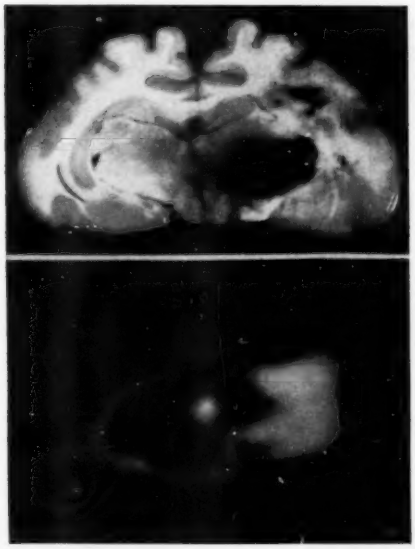


Fig. 7.—Radioautograph of cross section of cat's brain, two days after the development of a hemorrhagic infarct in the left hemisphere. P^{32} (0.6 mc.) was injected one day before death. Exposure time was 96 hours.

contralateral choroid plexus, although it was not directly involved in the injury. After four days the edema subsided and increased counts were restricted to the zone immediately adjacent to the paraffin plomb (Fig. 6). Hemorrhagic infarcts of two days' duration accumulated large amounts of P^{32} (Fig. 7).

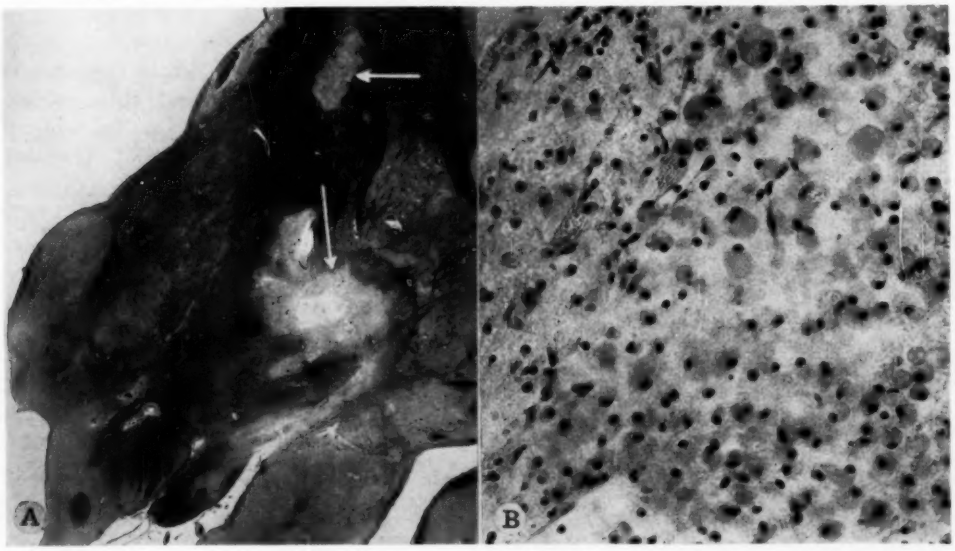
CEREBRAL INFARCTION IN HUMANS

Changes in the blood-brain barrier of humans in the area of cerebral hemorrhage or infarct have not been studied with vital dyes in vivo. Broman,[2] by perfusing the cerebral arteries shortly after death with a trypan blue solution, demonstrated perifocal staining in one case of encephalomalacia and one case of cerebral hemorrhage. The distribution of the dye exactly corresponded with the varying degree of demyelination. He considered this a strong argument for the assumption that the penetration of the dye during postmortem perfusion was actually caused by a disorder of the vascular permeability already present in vivo.

Bilirubin acts very much like vital dyes as far as its permeability through the blood-brain barrier is concerned. I recently studied the brain of a 77-year-old man who died of severe virus hepatitis.* This patient died two

* Detailed description of this case has been published in Case Records of the Massachusetts General Hospital, Case 40401 (*New England J. Med.* **251**:617-621, 1954).

Fig. 8 (Case N. T.).—*A*, myelin stain of the right basal ganglia showing the extent of the two areas of softening; Loyez stain; × 2.3. *B*, many phagocytes in the necrotic tissue; cresyl violet; × 267.



weeks after the onset of severe jaundice. At autopsy, an unsuspected infarct was found in the right frontal lobe, which caused no recognizable clinical symptoms. This infarct was at least one month old, and it was stained intensively by bile pigments. The rest of the brain was unstained except for a mild coloration of the choroid plexuses and ependyma of the ventricles.

The following case reveals the accumulation of P^{32} in a cerebral infarct of known duration:

N. T., a 67-year-old man (MGH-840297), suddenly developed left hemiplegia on March 2, 1954. Twenty-four days later he received a single intravenous injection of 3.7 mc. of P^{32}. The patient died five days after the injection.

gested a recent infarction, in good correlation with the clinical history.

Radioautographs of the corresponding cross section of the brain showed a local breakdown in the blood-brain barrier and accumulation of great amounts of the isotope in the necrotic areas (Fig. 9). The P^{32} content of various parts of the brain is given in Table 3.

COMMENT

It is known from earlier vital dye experiments that experimental or pathological injuries to the brain increase the permeability of the blood-brain barrier within the injured region. The best-documented investigations deal with the effect of direct artificial lesions on the permeability of the blood-brain barrier. Permeability changes of varying grade

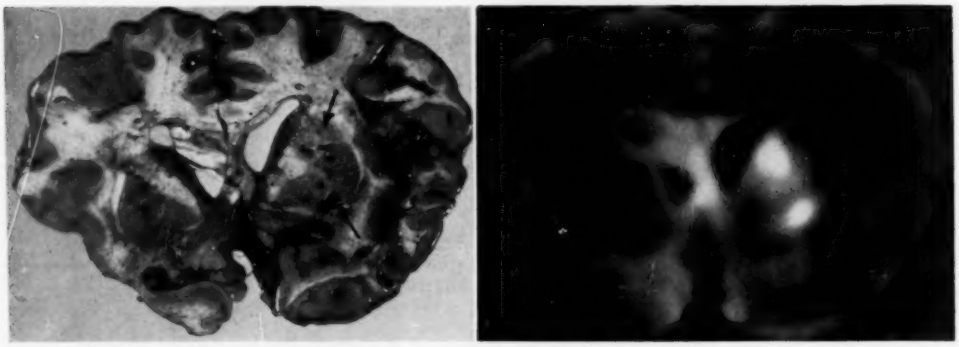


Fig. 9 (Case N. T.).—Radioautograph of coronal section of the brain. Arrows indicate the areas of necrosis. P^{32} (3.7 mc.) was injected intravenously five days before death. The specimen was 3 mm. thick. Exposure time was 67 hours.

Examination of the brain revealed encephalomalacia in the head of the right caudate nucleus. The right globus pallidus showed an area of softening which grossly appeared recent, and this softening extended into the adjacent internal capsule. A similar infarct was detected in the anterior part of the thalamus. The atherosclerosis of the cerebral vessels was severe.

Microscopic examination (Dr. E. P. Richardson) demonstrated an extensive lesion in the right internal capsule and basal ganglia (Fig. 8*A*). There were signs of beginning cavitation, but much of the necrotic tissue was not yet totally broken down. The diseased tissue contained large numbers of phagocytes (Fig. 8*B*), and within the lesion, as well as around it, the endothelial and adventitial cells of small blood vessels were swollen and proliferating. There was marked enlargement and proliferation of the astrocytes surrounding the areas of total necrosis. The appearance of this lesion suggested a recent infarction, in good correlation with the clinical history.

and duration followed simple exposure of the cortex (Grenell and McCawley[9];

TABLE 3.—*P^{32} Content of Various Parts of the Brain (Case N. T.)*

	P^{32} Content*
Plasma	4.3
Cerebral cortex	
1 mm. from surface	3.7
3 mm. from surface	2.7
5 mm. from surface	2.0
Deep white matter	0.9
Ventricular lining	2.7-3.0
Left (normal) caudate nucleus	3.5
Left (normal) putamen	1.7
Left (normal) internal capsule	1.5
Septum pellucidum	5.8
Center of necrotic areas	12.1-14.2
Marginal zone of demyelination	5.5-9.2

* Values are expressed in counts per minute per milligram of wet tissue.

Prados, Strowger, and Feindel,[20] but denied by Broman [3]), touching the surface of the brain with hydrogen peroxide (Givré and Rexed [8]), and coagulation of the intact dura (Caudill and co-workers [6]), as well as pricking, pressing, or contusion of the brain (Broman [3]). Severer changes were caused by cold or hot stabs or coagulation (MacCurdy and Evans [14]; Macklin and Macklin [15]; Mendel [16]; Broman, Radner, and Svanberg [5]; Moore [17]), by laceration of the brain (Syz [26]; Broman [3]), and by producing cerebral herniation with prolonged stasis and necrosis (Broman [3]).

All types of injury are not adequate to allow vital staining. King [12] pointed out that alteration of the barrier, that is, storage of trypan blue in parts of the nervous system where it does not normally occur, is dependent upon inflammatory or necrotizing changes. Other types of morphological changes, such as axonal degeneration or Wallerian degeneration, are not sufficient to allow vital staining (King,†). More recent experiments indicated, however, that "pure" impairment of the blood-brain barrier may occur without any attendant signs of edema and without the development of hemorrhages or necrosis. Such transitory increase in barrier permeability was produced by injecting certain contrast materials into the carotid artery (Broman and Olsson [4]) or by coagulating the external surface of the intact dura (Caudill and co-workers [6]).

The duration of the barrier breakdown in brain injuries was studied with vital dyes and was found to be proportionate to the severity of the damage. After a variable period of time the restitution of the wound and of the barrier reached the point when no more dye escaped through the capillary wall. Diffusibility of the different vital dyes also played a role in this process. The increased permeability of the blood-brain barrier lasted longer when tested with fluorescein than when tested with trypan blue (Moore [17]).

Broman's findings [3] with trypan blue can be summarized as follows: The increase in permeability did not exceed a few minutes following pricking of the cortex, contusion, or venous stasis of brief duration. The effect of gross pressure lasted 5 to 15 minutes. Microembolism with air had effect for one hour; with solid material, for about five days. Severer injuries, such as laceration, coagulation of the brain, or prolonged venous stasis with necrosis, increased the permeability for one week. According to Broman, Radner, and Svanberg,[5] the disorder in the permeability of the cerebral vessels following electrocoagulation is initially demonstrable over the whole of the damaged area. After a few hours, however, there is no more staining in the center of the lesion, because increasing stasis in the vessels prevents further circulation to the center. In the peripheral area of the damaged zone there were passable vessels which showed evidence of a disorder in their permeability lasting as long as one week subsequent to the damage.

The most complete study of vital dye deposition in experimental brain wounds and a microscopic description were made by Macklin and Macklin,[15] and their findings 34 years ago are worth recapitulating. They produced cerebral lesions in rats with heated needles and killed them at various intervals. Two days before death, except for experiments of shorter duration, the animals were given one or two parenteral injections of trypan blue. The staining of the injured tissue very rapidly reached its maximum brilliancy, usually six hours after injury, although they were already marked at the one-hour stage. The stain remained practically unimpaired until the end of the 3d day, following which it gradually faded, and by the 10th day it was quite weak. Afterwards it was practically negligible, although faint traces were observed in exceptional cases as late as the 35th day. Concomitant changes in the contralateral hemisphere (due to edema) lasted about four days. There were differences in the various zones of the lesion. The staining of the center of the lesion (the "coagulum"), in respect to its onset, duration, and disappearance, followed the scheme of the entire lesion. The staining of the necrotic

† References 10 and 11.

wall was quite comparable to that of the coagulum; it was a little more marked in the early stages—probably because of easier access to the dye through intact blood vessels. The vital staining of the macrophages on the second and third day was also a source of some accession in color in the necrotic wall at this time. At many later stages, such as that of the third day, after the dye had had time to diffuse into it, the coagulum stained more intensely than the necrotic wall, for in the latter absorption commences sooner, owing to better vascular organization. In the peripheral area, characterized by edema, the staining was strikingly milder than in the center and wall of the necrosis. Vitally stained mononuclear cells appeared in the necrotic region at the end of the second day and disappeared by the sixth day, or shortly thereafter. As compared with macrophages occurring in wounds of other tissue, these cells were remarkable for the small amount of dye they took up and the short duration of their staining. Many phagocytes contained no dye. The poorly stained peripheral zone of edema around the stab wounds also contained dead cells, especially around the needle tract. These stained densely with trypan blue in the early stages. However, most of the dye in this zone was extracellular.

The majority of the investigators believe that vital staining of injured areas of the brain results from an escape of the dye through the capillary wall. The influence of various factors on this process cannot be evaluated with certainty as yet. They may vary greatly according to the type and severity of the damage and also differ in the various zones around the center of the injured region. Broman [3] distinguished between direct mechanical damage to the capillary wall and a secondary toxic effect. The former causes many small vessels to rupture, and the result is an immediate leak in the barrier. The latter is the result of autolytic processes in the necrotic tissue, which presumably exert a secondary disturbing influence on the otherwise intact vessels and account for the persistence of increased permeability. This secondary toxic effect on the capillary wall by surrounding encephalomalacic tissue is held responsible for the barrier changes in cases of CO poisoning (Morgenstern and Birjukov [18]; Gullberg and Swensson ‡; Broman [3]). Locally increased venous pressure should also be mentioned as a third factor, which probably contributes to the increase in permeability by augmenting the hydrostatic filtration pressure.

A group of authors believe that the lack of vital staining of the central nervous system is based on lack of affinity of the cerebral tissue to vital dyes. In their opinion, through the injury the absorption relations of nerve cells are altered and staining occurs (Mendel [16]; Schmid [21]). King [12] believes that the primary cause of the accumulation of dye in a damaged focus is an intrinsic change in the tissue, leading to a heightened binding power. The actual alteration of the vascular wall might thus be of less importance than the change in the extravascular tissue, although there is no question that a capillary in an inflamed area is more permeable than normal.

Stern and Marshall [25] investigated P^{32} uptake in brains of cats with traumatic and ischemic lesions. The animals received an injection of the tracer 5 to 6 days after operation and were killed in 24 to 96 hours after the injection. Lesions produced by the electrosurgical unit showed dry weight assays 3.6 and 3.7 times higher than control tissue assays. The central portions of ischemic lesions counted 4.0 and 4.5 times higher than the opposite hemisphere.

My experimental findings reveal a striking similarity to those obtained by the use of vital dyes. However, P^{32} proved to be more sensitive an agent than vital dyes, and as a result increased permeability for this isotope persisted over a prolonged period of time following injury. The time curve of P^{32} concentration in the lesion as compared with that in the normal brain indicates that injury to the brain breaks down the blood-brain barrier and transforms the injured area into a "nonprotected" region, which is not dif-

‡ Gullberg, B., and Swensson, A., cited by Broman.[3]

ferent in this respect from any other organ of the body.

The peak of the local barrier breakdown was reached immediately after the injury and must be related to direct capillary damage. Autolytic changes in the surrounding tissues may add to the persistence of this phenomenon, but the decrease in P^{32} uptake, at the height of the macrophage activity in the lesion, indicates that these cells do not contribute, to any great extent, to the increased permeability. A clear-cut difference between a central area of destruction and a peripheral zone of edema is established in the first days. Afterwards the area of increased permeability is fairly uniform.

The pattern of P^{32} concentration in artificial space-taking lesions and in the human case of cerebral infarction is very similar to the pattern observed in brain tumor cases. The brain tumor material studied for P^{32} uptake in the department of neurosurgery of the Massachusetts General Hospital shows a great variation in tumor-normal brain ratio. Some astrocytomas were found to have only a very slight increase in their concentration of the tracer as compared with the surrounding tissue. However, the ratio of counts in the overwhelming majority of cases ranged from 5:1 to 100:1 (Selverstone, Sweet, White, and co-workers §). Much more consistent data were obtained on the uptake of various isotopes (including P^{32}) by brain tumors of mice studied under standard experimental conditions (Locksley, Sweet, Powsner, and Dow [13]). These investigators also performed continuous intracerebral probe counting of P^{32} in a human glioblastoma case. Their time curves of isotope concentration in the tumor and normal brain are strikingly similar to the time curves of lesion and normal brain in the present experiments. At the height of damage, the ratio of counts between the lesions and various parts of normal cerebral tissue in my experiments varied between 90:1 and 7:1. This corresponds to similar ratios observed in our brain tumor cases. In addition to its growth potential, the vascularity, vascular permeability, presence of necrosis or cyst formation, etc., all play a role in the P^{32} uptake of a tumor. However, it should be stressed that, whatever the other factors are, the high counts found in brain tumors could be explained theoretically by the increase of their capillary permeability. The only significant difference between tumor and traumatic lesion is that the change in barrier permeability in tumor is permanent, while, on the other hand, increased permeability of the blood-brain barrier in a traumatic lesion is transitory and is bound to decline as healing progresses.

§ References 22 through 24.

SUMMARY

The effect of cerebral stab injuries and artificial intracerebral space-taking lesions on the P^{32} concentration of the brain was studied in cats. The animals were killed in from 47 minutes to 42 days after the injury, having received single injections of the isotope 10 minutes following the injury in one group of experiments and 2 hours before death in another group.

Considerably higher amounts of the tracer were found in the injured area and in the surrounding edematous zone than in the normal brain. This local increase in the permeability of the blood-brain barrier was the greatest during the first hours after the operation, but it was still present six weeks afterwards. Time curves of P^{32} concentration in the lesion were compared with those for the normal brain. It was found that by destroying the blood-brain barrier for P^{32} by trauma the cerebral lesion has been converted into a "nonprotected" area, which does not differ in this respect from other tissues of the organism.

A human case is presented in which similar high concentration of P^{32} was detected in areas of cerebral infarction.

The results of these experiments are compared with similar investigations, in which vital dyes were used for indicators. The isotope findings are discussed with special regard to the application of P^{32} in the localization of brain tumors.

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WILSON'S DISEASE—CHRONIC FORM

Clinical-Pathological Observations in a Brother and Sister

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ALTHOUGH we deplore the general use of eponyms to designate disease entities, under certain circumstances an eponym is more informative than a purely descriptive clinical pathological term. Such is the case with Wilson's disease, in which the classic clinical triad of cirrhosis of the liver, degeneration of the lenticular nuclei, and Kayser-Fleischer rings has, in recent years, been somewhat overshadowed by the occurrence of massive amino-aciduria and increased urinary excretion of copper. The pathological designation of hepatolenticular degeneration is, in a sense, misleading, since the changes in the brain are certainly not limited to the lenticular nuclei. Wilson's disease generally appears in an acute or a chronic form, although sharp delineations cannot always be made. The chronic form is often mistaken for multiple sclerosis or chronic encephalitic Parkinsonism until its true nature is determined by the recognition of the characteristic pigmented ring at the corneoscleral junction and the clinical evidence of cirrhosis of the liver.

The chronic type has often been referred to as the pseudosclerotic form, but since the term pseudosclerosis is closely associated in the minds of most neurologists with the cases described by Westphal and by Strümpell, which Wilson [1] showed to be "cases . . . so heterogeneous as to be useless for the extraction of any specific clinico-pathological entity therefrom," the designation chronic is to be preferred. Wilson,[2] in his classic article in 1912, designated the disorder as "progressive lenticular degeneration, a familial nervous disease associated with cirrhosis of the liver." In the monograph by Hall,[3] the designation "Wilson's disease" appears for the first time.

The present study concerns a brother and sister aged 38 and 37 years, respectively, at the time of death, who suffered from the chronic form of Wilson's disease. The brother's illness was of more than 12 years' duration, and cerebellar symptoms were so prominent that, for many years, he was considered to be suffering from multiple sclerosis. The sister's illness was of at least seven years' duration, its onset being characterized by hemi-Parkinsonism. Both had Kayser-Fleischer rings and multilobular cirrhosis of the liver. In both, the lenticular nuclei were grossly normal, but a variety of alterations were noted in the basal ganglia, substantia nigra, brain stem, and cerebellum. Another sister, who exhibited tremor of the upper extremities, died suddenly of massive hematemesis, but four other siblings, as well as the parents, were symptom-free.

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REPORT OF CASES

CASE 1.—*History.*—S. R., a 38-year-old white man, was first seen by one of us in the neurology clinic of the Illinois Research Hospital on Dec. 29, 1937, at the age of 26 years. He stated that he had been more or less "nervous" for many years and that his hands were never too steady, but that, after an episode of mental stress eight months prior to admission, he had noticed tremor of his head and of his left upper extremity. He went to several physicians, who told him he was neurotic and advised psychotherapy. As his condition did not improve, he took chiropractic treatments and then visited a number of neurologists. He was originally considered to have a striatal syndrome and later to have multiple sclerosis. By November, 1939, action tremor appeared in all four extremities and the deep reflexes could not be obtained. The diagnosis of

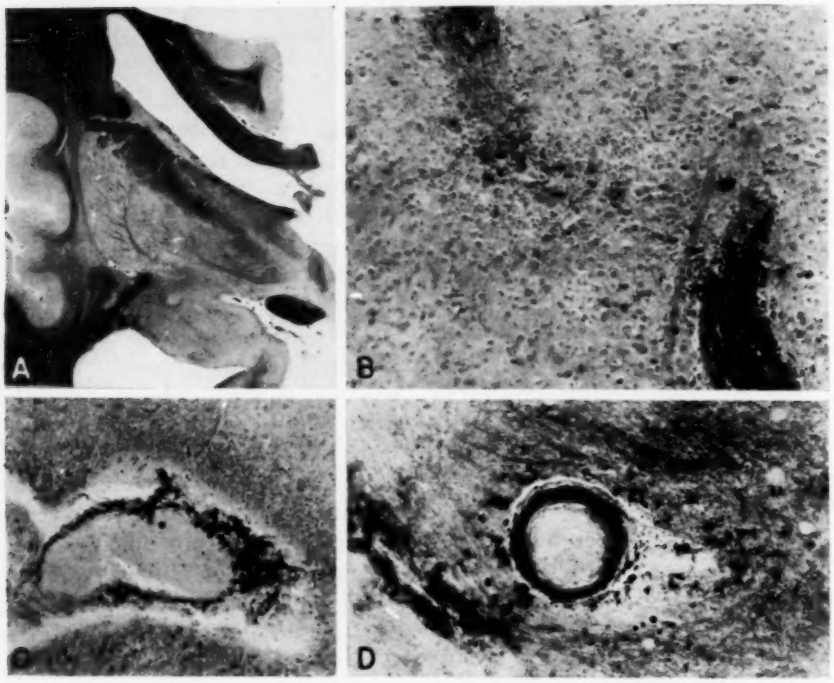
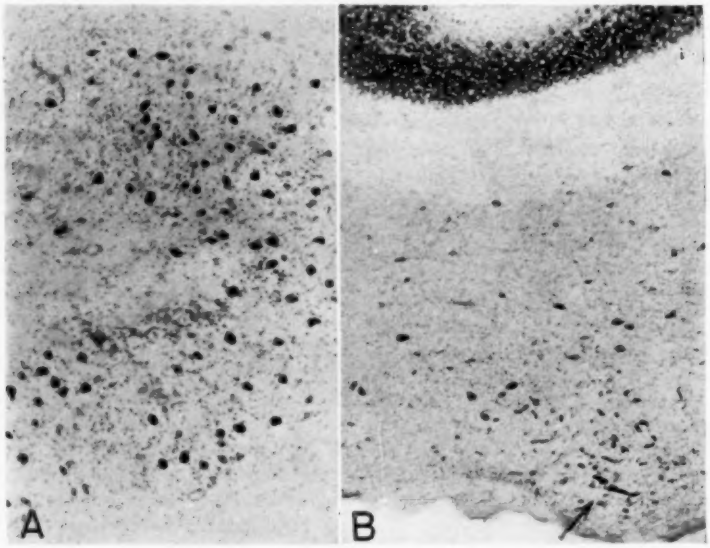


Fig. 1 (Case 1).—*A*, coronal section through the basal ganglia showing the absence of gross cavitation in Wilson's disease of 12 years' duration; Weil stain. *B*, rarefaction in the globus pallidus with a deficit in nerve cells and an increased deposit of blood pigment; Klüver stain. *C*, perivascular debris; oil red O stain. *D*, sclerosis of arterioles in pallidum; cresyl violet stain.

Fig. 2 (Case 1).—*A*, deficit of nerve cells and increased gliosis in the dentate nucleus. *B*, pericapillary concretions (arrow) in the roof nuclei. Cresyl violet stain.



Wilson's disease was established during a visit to the Mayo Clinic. He was subsequently seen in many neurological clinics, where the diagnosis was confirmed with the finding of the Kayser-Fleischer ring and evidence of dysfunction of the liver. He was hospitalized at the Research and Educational Hospitals, University of Illinois, five times for therapy and study. He complained of frequent nosebleeds and, on one occasion, suffered prolonged hemorrhage after a dental extraction. In addition to the scanning speech and action tremor, he presented cogwheel rigidity and head tremor. Both the static and the intention tremor were intensified when the patient was interviewed in front of a group of people. When admitted for the last time, in September, 1949, he was unable to speak or walk and had lost control of the urinary bladder and the bowel. He had repeated bouts of urinary tract infection, with elevated temperature and stupor. He showed both static and intention tremor, and his cogwheel rigidity had decreased in intensity.

Laboratory Studies.—Evidence of liver damage was present in the form of prolonged retention of sulfobromophthalein (Bromsulphalein) and a decreased prothrombin time. X-rays were not significant; all tests for syphilis on the blood and cerebrospinal fluid were negative, and the blood picture was within normal limits.

Gross Pathological Observations.—Brain: The leptomeninges over the convexity were thickened, and the brain stem and cerebellum were moderately atrophic. Coronal sections revealed symmetrical dilatation of the lateral and third ventricles and no evidence of gross destruction of the lenticular nuclei. Liver weighed 1350 gm. and was brownish-yellow in color, with a coarse hobnail surface. The surface made on sectioning revealed a disordered lobular pattern.

Microscopic Observations.—Brain: Microscopic study of representative areas of the cerebral cortex and subcortex failed to reveal any significant alterations. The hindbrain was cut serially, and representative sections were stained with the Weil and cresyl violet methods. The basal ganglia on the right side were cut serially in a horizontal manner, while those on the left side were cut serially in a coronal manner. Representative sections were stained with the Weil, cresyl violet, and Klüver methods. The basal ganglia, particularly the caudate and lenticular nuclei, were significantly atrophic (Fig. 1*A*). The general cytoarchitecture of the caudate nucleus was not altered but the cytoplasm of the smaller nerve cells stained poorly. Throughout the globus pallidus were many rarefied areas in which the nerve cells stained faintly or in which there was a great deficit of nerve cells and nerve fibers. In many of these foci one could see numerous deposits of blood pigment (Fig. 1*B*). In the lenticular nuclei, the perivascular spaces were enlarged and the adventitia was the seat of amorphous debris, blood pigment, and neutral fats. These substances were both free in the tissues and within macrophages (Fig. 1*C*). The arterioles in this region revealed medial sclerosis (Fig. 1*D*). Occasional large astrocytes with an ample amount of cytoplasm were seen in the degenerated areas. There was absence of inflammatory reactions and a significant lack of satellitosis or neuronophagia. The supraoptic and paraventricular nuclei were unchanged, as were the thalamic nuclei. There was no evidence of degeneration in the white substance, the centrum semiovale, the corpus callosum, the internal capsule, the anterior commissure, and the visual pathways being well stained in myelin sheath preparations. The compact zone of the substantia nigra revealed blood pigment and small quantities of melanin free in the tissues. The perivascular spaces in particular were the seat of considerable amorphous debris. Sections through the hindbrain revealed significant alterations. Some of the folds of the dentate nuclei exhibited a deficit in nerve cells and an increase in fibrillar glia (Fig. 2*A*). The perivascular spaces in both the central nuclei and the central white substance of the cerebellum contained considerable quantities of amorphous debris. In the region of the roof nuclei, the capillary blood vessels were encrusted with beads of what appeared to be calcific material (Fig. 2*B*). Identical pericapillary concretions, but of far greater intensity, were observed in symmetrical sites of the medulla oblongata at the level of the inferior olivary bodies, the changes being roughly limited to the acoustic tubercle and its environs (Fig. 3). The amorphous material stained lightly for calcium and iron but heavily for copper with Mallory's method. The cerebellar cortex was not significantly altered, and sections from representative levels of the spinal cord were not abnormal.

Liver: The capsule was thickened throughout, and there was a multilocular cirrhotic pattern. Many of the liver cells in the neighborhood of the central vein were atrophic or necrotic, and there was a considerable degree of fatty metamorphosis. There was a moderate degree of proliferation of the bile ducts.

Anatomical Diagnosis.—(1) Brain changes of Wilson's disease; (2) multilobular cirrhosis of the liver; (3) Kayser-Fleischer rings; (4) splenomegaly; (5) dilated esophageal veins, and (6) severe bronchopneumonia of both pulmonary lobes.

CASE 2.—*History.*—I. G., a 38-year-old, married white woman, was first seen by one of us in the outpatient clinic of the Mount Sinai Hospital of Chicago in 1946, at which time the clinical picture was that of right-sided hemi-Parkinsonism characterized by masked facies and rhythmical tremor, greater in

the upper extremity. When it was learned that a sister who had tremor of the hands had died suddenly after massive hematemesis (of esophageal varices) and that her brother was S. R. (Case 1), the eyes were scrutinized and golden-brown discoloration of the corneoscleral junction was seen bilaterally. The patient was next seen in the Research and Educational Hospitals of the University of Illinois in December, 1951, at which time she exhibited both static and action tremor of both upper extremities of such severity that she was unable to write or perform fine movements. She stated that six months previously the tremor had spread to involve the right lower extremity and that she also noticed edema of the ankles and an increase in her abdominal girth. She was decigravida, sextipara, with five living children, all well, four spontaneous abortions, and one infant death, from pneumonia.

Examination at this time revealed, in addition to the classic Kayser-Fleischer rings, moderate obesity, spider hemangiomata of the anterior chest wall, hesitant speech, static and action tremor of both upper extremities, normal cranial nerves, absence of sensory disturbances, normal superficial and deep reflexes, and normal plantar responses. Examination of the upper alimentary tract with barium revealed extensive varices in the lower third of the esophagus.

She was readmitted in February, 1952, at which time her speech was noted to be more hesitant. Pneumoencephalography demonstrated a normal ventricular system, and electroencephalography showed reduced amplitude in the left hemisphere. Psychometric studies showed her intelligence to be low average, and there was considerable emotional lability. The cephalin flocculation test was 4+ and the thymol turbidity test 13 units. Chemical analysis of the urine revealed 153 γ of copper in a 24-hour specimen. After administration of dimercaprol U. S. P. (BAL) the copper excretion rose to 1,530γ per liter. Because of burning paresthesias of the mucous membranes, the dimercaprol was discontinued for a time. With the administration of 200 mg. of dimercaprol, I. M., daily for nine days, the excretion of copper in the urine was determined to be 625γ per liter. Following almost daily administration of 200 mg. of dimercaprol, I. M., in March, 1952, there was considerable improvement in the clinical picture. The patient could feed herself, and the tremor was so much less intense that she could apply lipstick.

In June, the swelling of the ankles and the distention of the abdomen were more marked, and she was treated with a low-salt diet and meralluride U. S. P. (Mercuhydrin). Her third admission to Research and Educational Hospitals was in December, 1952, after which she was administered another course of dimercaprol. In March, 1953, it was noted that, although the objective tremor was not improved, the patient could knit, whereas she had not been able to do so for several months before. Her fourth admission to Research and Educational Hospitals was in June, 1953. Examination then showed marked ascites and ankle edema. The mood was euphoric; the speech scanning, and the tremor had increased in intensity. The patient became agitated and depressed, cried at the slightest provocation, and failed to respond to therapy. She was discharged to her family and taken to a nursing home. On June 24, 1953, her condition became grave, and she was taken to the Mount Sinai Hospital of Chicago. Her temperature fluctuated from 100 to 106 F., and there were multiple decubiti on the hips, back, and elbows. Despite supportive therapy, she never rallied, and she died 15 days after admission.

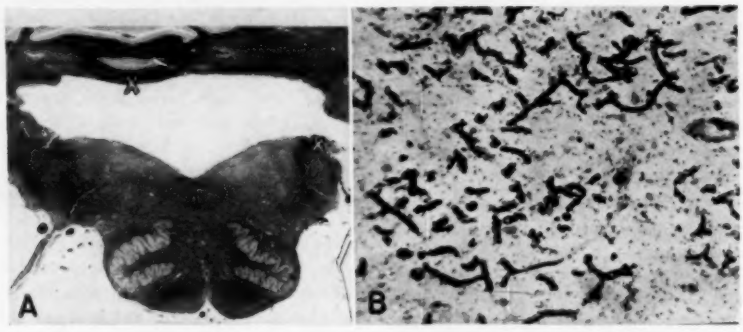


Fig. 3 (Case 1).—*A*, pericapillary concretions (×) in the cerebellum and medulla oblongata; Weil stain. *B*, detailed histology of the pericapillary beading and sheathing; Mallory's stain for copper.

Gross Pathological Alterations.—Brain: External surface was not significant, but coronal sections revealed focal and confluent hemorrhages in both internal capsules and smaller focal hemorrhages in the centrum semiovale (Fig. 4*A*). Sections through the midbrain revealed massive confluent hemorrhages in the region of the substantia

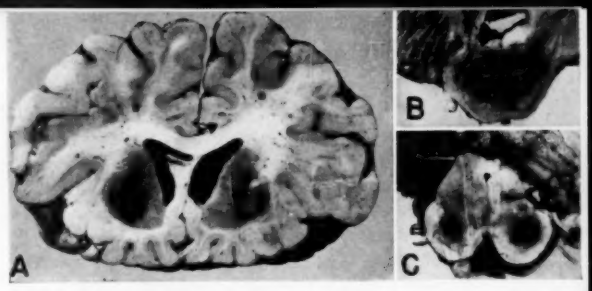


Fig. 4 (Case 2).—Gross hemorrhages in the internal capsules, the midbrain, and the pons.

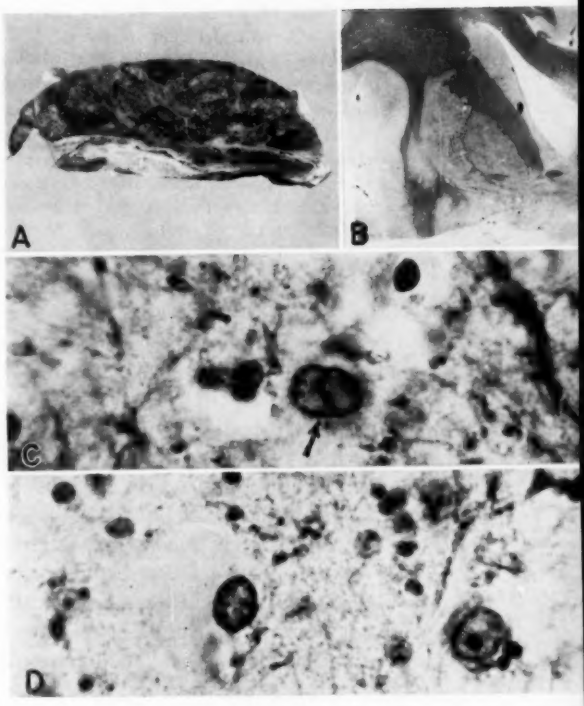


Fig. 5 (Case 2).—*A*, multilobular cirrhosis of the liver. *B*, lack of gross cavitation in the lentiform nucleus; Klüver stain. *C* and *D*, high-power photomicrographs showing the large astrocytes in the lenticular nuclei and the characteristic Alzheimer glia cell (arrow) in *C*; Klüver stain.

nigra and environs, and sections through the hindbrain revealed symmetrical hemorrhages in the pons and single hemorrhagic areas in the white substance of the vermis (Fig. 4*B* and *C*). Liver was markedly reduced, weighing 800 gm. The external surface was coarsely nodular, the nodules varying in size from 1 to 3 cm. The surface made on sectioning revealed greenish-brown, bulging nodules, separated by a fine network of grayish fibrous connective tissue (Fig. 5*A*). The basal ganglia were grossly normal, no cavitation being seen in the lenticular nuclei (Fig. 5*B*).

Microscopic Observations.—Brain: The leptomeninges were thin and free of cellular infiltrations. The cytoarchitecture of representative areas of the cerebral cortex was well preserved, as was the white substance in the subcortex, centrum semiovale, corpus callosum, and fornix. In the corpus striatum, at the level of the anterior limb of the internal capsule near the hemorrhages, the myelinated nerve fibers showed degenerative changes, being permeated with numbers of macrophages. The caudate nucleus showed an increased cellularity, the cells being, for the most part, neuroglia and macrophages filled with granules of pigment material. The nerve cells of the caudatum were well preserved. In the putamen, granules of blood pigment were scattered in the ground substance, and discrete deposits were found within the nerve cells. Occasional large astrocytes were observed, some having a kidney-shaped nucleus, while others had an ample quantity of cytoplasm (Fig. 5*C* and *D*). The external capsule and claustrum revealed similar deposits of blood pigment.

Nissl preparations of the midbrain revealed striking changes. The compact zone of the substantia nigra on one side was degenerated, the large nerve cells being replaced by a dense glial scar, and within the gliotic area were nests of encrusted and obliter-

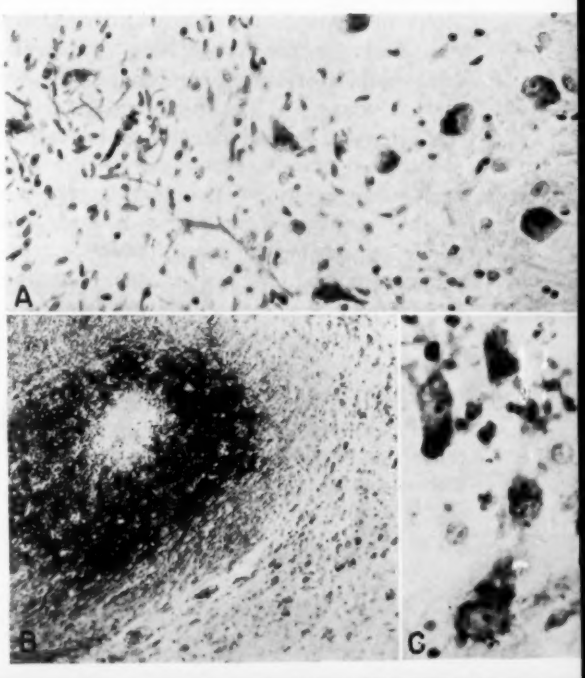


Fig. 6 (Case 2).—*A*, degenerative changes in the substantia nigra. *B*, ring hemorrhage in pons. *C*, hematoidin granules within nerve cells in nuclei pontis. Cresyl violet stain.

ated capillary blood vessels (Fig. 6*A*). There were no inflammatory reactions. In the pons, there was evidence of recent and old hemorrhages, the recent hemorrhages being circular or ring-like, centering about veins (Fig 6*B*). The cytoplasm of many of the nerve cells in the nuclei pontis was stuffed with hematoidin granules (Fig. 6*C*). The cerebellum presented a normal-appearing cortex, but the white substance of many of the folia near the solitary hemorrhage was the seat of recent softening.

Liver: There was a marked increase of the fibrous stroma circumscribing large nodular areas, which included numbers of lobules. There were an increased number of bile ducts, and the liver cells showed degenerative changes. Many of the cells contained large fat droplets, while others were necrotic. The smaller biliary radicles were distended with bile.

Anatomical Diagnosis.—(1) Brain changes of Wilson's disease; (2) multilobular cirrhosis of the liver; (3) Kayser-Fleischer rings.

COMMENT

The association of cirrhosis of the liver with brain damage has been one of the enigmas of modern medicine. Many authorities believe that the liver damage is responsible for the changes in the brain, but the evidence is far from conclusive in such a specific disorder as Wilson's disease. Baker [4] studied the central nervous system in 18 cases of acute, subacute, and chronic liver disease and found extensive changes in 8 cases. The alterations were predominantly perivascular, in the nature of nerve cell damage and demyelination, and were attributed to an unknown toxin.

Hemorrhagic State.—Hepatic insufficiency may produce a hemorrhagic state, with resultant petechiae or large hemorrhages (Stokes and associates [5]). The focal and confluent hemorrhages throughout the brain in our second case may have been due to liver disease. It is interesting to note that the patient's brother suffered from repeated nosebleeds and extensive hemorrhage after the extraction of a tooth. Lüthy [6] called attention to the development of purpura in instances of hepatolenticular degeneration and concluded that a hemorrhagic diathesis is not a rare symptom of Wilson's disease. Massive hematemesis from esophageal varices is the result of portal hypertension, and not necessarily related to liver dysfunction per se.

Biochemical Aspect.—In recent years, the emphasis in Wilson's disease has shifted from its morphology to its biochemistry. In 1948 Uzman and Denny-Brown [7] called attention to the massive amino-aciduria found in a case of Wilson's disease with minimal liver damage and postulated a fundamental defect in amino acid metabolism in this disorder. The urinary amino acid abnormality has been clarified by the work of Moore and Stein,[8] who demonstrated a considerable increase in the excretion of many of the amino acids found in normal urine. Whereas some amino acids were excreted in amounts close to the normal range, two amino acids not found in normal urine were frequently present.

Haurowitz [9] (1930) noted the increased copper content of the brain and liver in Wilson's disease, and this observation was confirmed by the studies of Glazebrook [10] and Cumings.[11] Mandelbrote and associates[12] (1948) showed that dimercaprol could produce an increased urinary excretion of copper, and this was tried by a number of investigators.[13] Our second patient had several courses of treatment with dimercaprol, with a resultant marked increase in the urinary excretion of copper and an improvement in the clinical picture, but the benefits were short-lived. Whereas there is an increase in the urinary excretion of copper in Wilson's disease, the copper content of the blood serum is low. Scheinberg and Gitlin [14] suggested that Wilson's disease is the result of a deficiency in a specific plasma protein (ceruloplasmin) and that, as a result, an increased quantity of copper is absorbed from the intestinal tract and deposited in the tissues. The temporary clinical improvement in the neurological picture and the increased excretion of urinary copper suggest that the copper is loosely bound to the neural tissues and easily displaced by a chelating agent, such as dimercaprol. The final chapter in the biochemical abnormality in Wilson's disease has not been written, but it appears from studies by Uzman [15] that the increased urinary excretion of copper and the increased and abnormal amino-aciduria are two dis-

tinct, but probably mutually complementary, factors responsible for the brain and liver changes.

Brain Changes.—One must repeat that the use of the term hepatolenticular degeneration is more misleading than informative, for it leads many to believe that the changes in the brain are limited to the lenticular nuclei. We have seen many instances in which the diagnosis of Wilson's disease was not even considered because of the presence of cerebellar and Parkinsonian symptoms and signs. In the original thesis by Wilson, emphasis was laid on the lesion of the lenticular nuclei, but in the 1941 edition of his "Neurology" attention was already called to lesions in other portions of the brain. The two cases we describe have been designated by some as the chronic, or pseudosclerotic, form. In many of these instances, there is no gross cavitation of the lenticular nuclei, but microscopic study shows a deficit in nerve cells, degeneration of nerve fibers, considerable quantities of amorphous debris, and shrinkage of the nerve tissues, with enlargement of the perivascular spaces. So-called giant glia cells of Alzheimer were observed microscopically in both cases, but they were not common and had to be looked for. Of greater interest were the pericapillary beading and sheathing in the dorsal lateral portion of the medulla oblongata, chiefly the acoustic tubercle, and in the vermis of the cerebellum. Although histochemical methods on formalin-fixed tissues are not too reliable, the pericapillary sheathing which appeared superficially as calcifications proved to give a positive stain for copper with Mallory's method. Identical changes were seen in the study by Lüthy.[6]

The pericapillary beading and sheathing which appeared to be "calcifications" in hemalum and eosin preparations were identical to the changes seen in the Sturge-Weber-Dimitri syndrome (Lichtenstein [16]). In an earlier work (Lichtenstein and Rosenberg [17]), attention was called to the fact that what appears as calcifications are often admixtures of calcium salts and other elements, and in some instances the other element is iron. In our cases the calcium was mixed with copper, a finding which is in harmony with the increased copper content of the brain in Wilson's disease. The histodynamics of all these calcareous deposits appears to be a metabolic disturbance resulting in the deposition of a colloidal substance which later becomes the nidus for the deposition of calcium, iron, copper, and possibly other elements.

The degeneration of the substantia nigra on one side in Case 2, in which the clinical picture began with signs of hemi-Parkinsonism, emphasized the clinical-anatomical relationship seen in chronic encephalitic Parkinsonism. Instead of inflammatory phenomena, however, there was vascular change, gliosis, and degeneration of the pigmented nerve cells of the compact zone. In the second case, in which multiple terminal and preterminal hemorrhages complicated the pathological picture, the basic lesions of Wilson's disease could be discerned, despite the absence of gross degeneration of the lenticular nuclei.

The pallial component of Wilson's disease was not present in our cases. In a comprehensive article on this phase of the pathological process by Richter,[18] attention was called to the necrotizing changes involving both cerebral cortex and convolutional white substance. The reports by Ostertag [19] and by Bielschowsky and Hallervorden [20] support the view that the pallial changes are basic phenomena in Wilson's disease, but whether they are related to the fault in copper and amino acid metabolism or to secondary changes incident to severe damage of the liver has not been established with certainty.

Clinical Features.—From a review of the clinical histories it is evident that both cases represent the chronic form of Wilson's disease. Since the clinical picture may resemble that of multiple sclerosis, the term pseudosclerosis has been applied, but there is no advantage in such a designation. Tremor of action, or the so-called intention type, is a constant clinical sign, and this is much more marked than that seen in an average case of multiple sclerosis. The action tremor

involves large muscle groups concerned with axial and para-axial movements, such as the muscles of the spine and the girdle, with resultant flapping or flying movements of the outstretched upper extremities. These patients have great difficulty in feeding themselves, and the tremor, being increased by voluntary movement, has often been designated as cerebellar in type. The basic anatomical site for such a motor phenomenon is a lesion in the dentorubral system, and the degenerative changes in the dentate nuclei in Case 1 lend support to such an anatomical-clinical correlation. In the second case, the onset was with the classic symptoms of chronic encephalitic Parkinsonism and the degenerative changes in the substantia nigra lend support to another anatomical-clinical correlation. In short, the clinical picture in the chronic form of Wilson's disease is far from that seen in a lesion confined to the lenticular nuclei, and the realization that the pathological process may be elsewhere in the nervous system is of the greatest importance. Both our cases had prominent Kayser-Fleischer rings, and it has been stated that this has been uniformly present in all instances of the chronic variety of Wilson's disease. As such, it is a most important clinical sign in the recognition of a disorder which may superficially appear to be a combination of multiple sclerosis and chronic encephalitic Parkinsonism. The beneficial response to dimercaprol was most encouraging in our second case, but it became evident that the drug did not offer a cure and relapse was severe after each course of therapy.

The absence of clinical evidence of dysfunction of the liver in a disease which almost uniformly presents anatomical evidence of intense cirrhosis has been another distressing feature of Wilson's disease. Except for terminal hematemesis, signs of liver disease were generally lacking until the colloidal gold reaction [21] of blood serum was introduced. The development of clinical tests which serve to widen the spectrum of the liver profile, has aided materially in the detection of liver dysfunction in Wilson's disease.[22] In a recent review of 11 cases by Franklin and Bauman,[23] the conclusion is reached that frank hepatic decompensation is common in Wilson's disease, and laboratory confirmation was found in 7 cases.

SUMMARY

The clinical and pathological features of the chronic form of Wilson's disease in two siblings are presented.

There was no gross evidence of cavitation of the lenticular nuclei, but microscopic changes in the form of nerve cell degeneration, shrinkage of the brain tissue with enlargement of the perivascular spaces, and the deposition of lipids, blood pigments, and amorphous debris were present.

Pathological alterations were observed in the dentate nuclei, the substantia nigra, and the medulla oblongata. Pericapillary beading and sheathing with calcareous material gave positive stains for copper with Mallory's method.

Cerebellar and Parkinsonian signs and symptoms are common in the chronic, or pseudosclerotic, form of Wilson's disease.

Remissions occurred in one instance with dimercaprol therapy, but relapses were severe.

Hemorrhages may occur in Wilson's disease as the result of esophageal varices or from a hemorrhagic state induced by dysfunction of the liver. The hemorrhagic state may complicate the changes in the brain and lead to a complex pathological picture.

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RESPIRATORY PROBLEMS IN ACUTE GUILLAIN-BARRÉ SYNDROME

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SINCE 1916, when Guillain, Barré, and Strohl [1] described two cases of radiculoneuritis with special findings in the cerebrospinal fluid (albuminocytologic dissociation), acute radiculitis has received attention throughout the world, innumerable cases having been described in the literature. Guillain's two cases were purely spinal with tetraplegia, and the prognosis quoad vitam did not come into question. But in acute polyradiculoneuritis nerves of vital importance may be attacked, i. e., the vagus, phrenic, and intercostal nerves. In such malignant cases the prognosis quoad vitam is serious, and in the literature the mortality rate varies between 15% and 75% in undifferentiated series.*

During the period from 1947 to March, 1953, the Stockholm Hospital for Infectious Diseases had a total of 15 cases of acute malignant Guillain-Barré syndrome attended by pharyngeal and respiratory paralysis, the patients comprising 11 adults and 4 children aged from 3 to 13 years. Seven (47%) of these patients required respirator treatment, and all of them died; the mortality was thus 100% in the respirator cases. In the remaining eight patients regression occurred at the critical peak stage and artificial respiration was unnecessary. The respirator employed in each of the seven fatal cases was a cuirass model of Stille type, i. e., a body respirator with intermittent negative pressure.

The poor prognosis quoad vitam is in striking contrast to the very good prognosis with respect to restitution of the paralysis.[6]

The etiology of acute polyradiculoneuritis is exceedingly varied and in most cases quite unknown, but the symptomatology in malignant cases is fairly consistent. The disease runs a relatively rapid course, usually about a week, and progresses toward a crisis, at which point it may be abruptly halted and then regress. The Landry type of paralysis is common. When the process commences to attack the pharyngeal and respiratory motor nerves, a life-endangering condition results. In pharyngeal paralysis quantities of mucus and saliva are formed which cannot be swallowed in the normal way but stagnate in the pharynx and run into the trachea and bronchi, with a major risk of obturation of the air passages. If the respiratory motor nerves commence to fail, there will be a threat of ventilatory insufficiency and respiratory standstill.

The condition in these malignant cases with pharyngeal and respiratory paralysis is similar to that in poliomyelitis, and the treatment, too, is largely the same. If patients with these malignant types of polyradiculitis are to survive the crisis, it is essential both to keep the air passages free by preventing aspiration of mucus and saliva and to give adequate artificial respiration, which implies sufficient oxygenation as well as elimination of carbon dioxide.

Serious deficiencies in the above respects were doubtless the principal cause of lethal outcomes in many malignant cases of Guillain-Barré syndrome with pharyngeal and respiratory paralysis.

To illustrate these considerations, a few typical cases which I personally studied are reported below.

REPORT OF CASES

CASE 1.—Man, 46. In October, 1942, the patient had acute numbness and paresthesias of the hands and feet and increasing weakness of the arms and legs. On admission, the fourth day after the onset, he showed facial diplegia, tetraplegia, areflexia, and distal impairment of sensibility. After a few days there were supervenient pharyngeal paralysis with stagnation of mucus in the pharynx, a feeble

From the Stockholm Hospital for Infectious Diseases.

* References 2 through 5 and 7.

cough, and incipient respiratory paralysis, which rapidly increased. The patient, in poor general condition and with severe cyanosis, was placed in a cuirass respirator, lost consciousness, and died with gurgling mucus in the pharynx.

At autopsy the trachea and bronchi were found to be almost filled with thin, frothy, turbid and viscous mucus; the lungs were highly edematous and in parts showed small bronchopneumonic foci. The heart and other organs presented no appreciable disease aside from general stasis and cyanosis.

CASE 2.—Man, 23. In November, 1949, the patient had acute numbness and paresthesias of the hands and feet and incipient muscular weakness in the extremities. After two days there was tetraplegia with areflexia and loss of sensibility, as well as partial paralysis of the pharynx and vocal cords, with profuse formation and stagnation of mucus in the pharynx. On the third day, total paralysis of the pharynx with large amounts of mucus, the patient being placed in Trendelenburg's drainage position. On the fourth day, incipient respiratory paralysis, which showed rapid progression. Twenty-four hours later the respiration was acutely impaired and the patient, in a moribund condition, was placed in a cuirass respirator of Stille type. He died a few minutes later.

Autopsy revealed general cyanosis of the organs, and atelectasis of both lower lobes, with small pneumonic infiltrations; the trachea and bronchi were filled with mucus, which in parts caused total occlusion.

CASE 3.—Three-year-old girl. In November, 1947, the patient had acute pain and weakness in the legs and was admitted on the suspicion of poliomyelitis. She showed profuse mucus formation and redness in the pharynx on admission, but no demonstrable pharyngeal paralysis; however, there was paralysis of the trunk and extremities, areflexia, and distal impairment of sensibility. The child was whimpering and had a spasmodic cough. The blood pressure and pulse were pathologically elevated. Progression occurred, and after a week there was total paralysis with profuse mucus formation stagnating in the pharynx. Respiratory paralysis developed and progressed toward a critical condition, the patient becoming subcomatose and cyanotic, with scarcely perceptible, rattling breathing and large moist rales over the lungs. She was immediately placed in a cuirass respirator but soon died.

Autopsy, 72 hours later, showed general cyanosis of the organs and small basal atelectatic areas in the lungs, with occasional mucopurulent bronchial plugs and reddened bronchi. The viscera, including the heart, otherwise showed no appreciable disease.

CASE 4.—Girl, 17. In September, 1952, the patient had acute muscular weakness in the extremities, as well as distal numbness and paresthesias. On admission she presented tetraplegia, areflexia, and distal loss of sensibility. During the next few days the paralysis progressed, and after a week there was tetraplegia, paralysis of the trunk, facial diplegia, and partial pharyngeal paralysis with profuse mucus formation in the pharynx. The patient was placed in the abdominal drainage position, and removal of the thick mucus by suction brought about a transient improvement. Respiratory paralysis supervened and progressed. The patient was submitted to tracheotomy and bronchoscopy, and after insertion of a silver cannula she was placed in a cuirass respirator. Her condition improved, but only for a short time. In the further course she was repeatedly in danger of asphyxiation, with elevation of the blood pressure; there were also states of shock with falls in the blood pressure, indicating daily removal of purulent secretion from the trachea and bronchi through the bronchoscope. The condition progressively worsened, the patient dying in the respirator four weeks after the onset.

Autopsy disclosed pronounced ulceration of the tracheal mucosa, the cartilaginous rings being exposed in parts, as well as severely swollen mucosa and large amounts of mucopurulent secretion in the right bronchus. Large atelectatic areas were present in both the upper and lower lobes of both lungs. There were bronchopneumonic foci bilaterally. The rest of the viscera were severely cyanotic.

Each of the above cases presented respiratory paralysis and obstruction of the respiratory tract by copious amounts of secretion which could be neither swallowed nor expectorated. Pharyngeal paralysis was definitely present in the adults, but only probable in the 3-year-old child. All four patients died in body respirators. In the fourth case efforts were made up to the last moment to free the respiratory tract from obturating secretion by tracheotomy and suction through the bronchoscope, and in this way the patient's life was prolonged for a time. Repeated aspiration gave rise to purulent bronchitis with severely swollen mucous membranes, which ultimately made effective drainage impossible, the patient dying of extensive pulmonary atelectasis, purulent bronchitis, and pneumonia. The other patients died a few hours at the most after being placed in the respirator.

Two of the patients (Cases 1 and 3) also had pulmonary edema. In one of them this fact was verified at autopsy, which took place within 24 hours; in the other it was verified only clinically before the respirator was resorted to. In the latter case autopsy was de-

layed for three days, which fact may explain the relatively meager autopsy findings.

The cause of the pulmonary edema lies partly in cardiocirculatory factors, partly in unfavorable pressure in the lungs, and partly in hypoxic damage to the capillaries of the lungs. Cases with vagus involvement regularly present tachycardia, with pulse rates up to 150. The tachycardia is mainly attributable to a state of unbalance between the depressor and accelerator components of the mechanism regulating the heart, the latter component predominating because of the vagus involvement. It may, however, be partly due to acute myocarditis. It is a surprising fact that myocarditis occurs in the Guillain-Barré syndrome. Haymaker and Kernohan reported histologically demonstrable focal myocarditis in 7 of 50 autopsy cases of Guillain-Barré syndrome.[7] In the present series acute myocarditis was observed electrocardiographically in at least three cases. The myocarditis may, however, be caused by hypoxic damage to the myocardium in the cases with respiratory insufficiency. If acute myocarditis is present, there will be the risk of an acute fall in the cardiac output, with ensuing peripheral shock and pulmonary stasis with edema.

Free air passages constitute a fundamental problem in the treatment of cases with respiratory paralysis. Owing to the frequently coexistent pharyngeal paralysis there is an imminent risk of respiratory tract obstruction, since saliva and profuse mucus cannot normally be swallowed or expectorated. Drainage of mucus and saliva will be necessary as soon as dysphagia develops. This drainage can be conveniently effected, at an early stage before respiratory paralysis supervenes, by placing the patient in an inclined abdominal drainage position, for which a special drainage bed has been designed.[8] If progression occurs with paralysis of respiratory motor nerves and threatened ventilatory insufficiency, so that artificial respiration has to be resorted to, it is of the greatest importance to ensure free air passages by tracheotomy and intubation with a rubber tube or a silver cannula having a cuff, which occludes the passage around the tube or cannula. When this has been done, artificial respiration can be resorted to. As regards artificial respiration, the essential thing is that it must ensure adequate ventilation and must not have a deleterious effect on the circulation. Current respirators of tank and cuirass type operate by intermittent negative or negative-positive pressure over the body. This type of artificial respiration is sufficient in many cases, especially in the subacute and chronic stage. In the severe cases during the acute stage, however, the body respirators have not proved fully adequate to compensate for the ventilatory insufficiency. For such severe acute cases artificial respiration by direct endotracheal insufflation is to be recommended as a more reliable method. This method must, however, conform to physiologic principles of respiration and circulation; i. e., it must not have a deleterious effect on the cardiac output. On the basis of such principles a respirator was recently designed at the Stockholm Hospital for Infectious Diseases by Dr. Carl-Gunnar Engström.[9]

ENGSTRÖM RESPIRATOR

The Engström respirator has a double action and provides endotracheal positive pressure inspiration and active expiration, either by compression of the thorax by an inflatable girdle or by direct suction in the air passages. The respirator operates by volume-time cycling, i. e., gives an adjustable gas volume in the same unit of time. It has no CO_2 absorber but has a special valve system with a double-acting expiratory valve, governed by the variations of pressure in the insufflation system. An extra inspiratory valve permits of spontaneous breathing independently of the rhythm of the respirator. The insufflated ventilatory volume can be regulated, like the respiratory frequency and the inspiratory rate of flow. An adjustable water lock indicates the inspiratory pressure in the air passages, thus ensuring that the latter will be free and not obstructed and preventing dangerous positive pressure. Owing to the active expiration by the girdle on the thorax or by the direct suction in the air passages, provided by a Venturi attachment to

the expiratory valve, the insufflation pressure can be lowered with the same minute ventilation. In this way the mean inspiratory pressure can be kept at a low level, facilitating the venous return and preventing shock. The insufflation unit permits administration of air and oxygen, or any other mixture of gases in any proportions. The insufflated gas is heated and highly humidified.

The Engström respirator constitutes a considerable advance in the technique of artificial respiration, especially for severe acute cases of respiratory and cardiocirculatory insufficiency of varying etiology. The respirator has been used with great success in the acute stage of severe poliomyelitic respiratory paralysis, chiefly in cases with bulbar involvement, as well as in other medical and surgical or neurosurgical cases with respiratory arrest.[10]

The method of treatment, mentioned above, with tracheotomy, intubation, and artificial respiration by the Engström respirator has been used in a case of Guillain-Barré syndrome with pharyngeal and respiratory paralysis, which case is reported below.

Woman, 28. The disease was ushered in on April 2, 1953, with acute numbness and paresthesias of the hands and feet, as well as headache and vertigo. There was relatively rapid development of flaccid paralysis of all the extremities, with generalized areflexia, facial diplegia, and distal hyposensibility. Thirteen days after the initial symptoms, slight respiratory distress and dysphagia developed. The respiratory paralysis progressed, and after two days there was only very slight spontaneous breathing and increasing cyanosis. On admission, patient was subcomatose, cyanotic, with only very slight thoracic and no diaphragmatic breathing, and showed peripheral coldness. The right half of the thorax was immobile, pointing to atelectasis. High tracheotomy was promptly done, large amounts of thick grayish-white secretion (probably aspirated milk) being removed from the right main bronchus via the bronchoscope. Rüsch tube No. 11 was inserted through the tracheotomy and, after 30 minutes of manual positive pressure respiration by an absorber system, the Engström respirator was connected to the intubation tube (Fig. 1). Pure oxygen was administered for the first hour, but after that a 50% mixture of air and oxygen with a minute ventilation of 8 liters. This rapidly produced a considerable improvement, with good color and peripheral warmth. During the next 24 hours repeated aspiration of the bronchi was done with a soft catheter via the intubation for the bronchoscope, large amounts of white turbid secretion being removed. Three days after the critical stage the paralysis commenced to abate and feeble spontaneous breathing and swallowing function returned.

Figure 1.

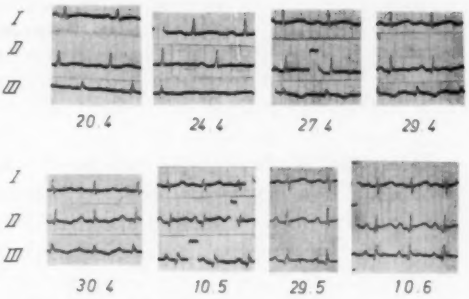

Fig. 2.—Electrocardiograms show progressive changes in the terminal complex, shifting of the electrical axis, and widening of QII-III, pointing to necrotic myocardial damage, and splintering of RII as in intraventricular block. Flattening of the S-T wave may point to concomitant pericarditis.

Since the patient had tachycardia—the heart rate being up to 140—an electrocardiogram was taken and showed signs of acute myocarditis. Further electrocardiograms during the next week showed progression of the myocarditis (Fig. 2). On the 10th day there was an exacerbation, the patient complaining of cardiac pain and having cyanosis, a pulse rate about 130, and blood pressure of 245. A spontaneous improvement occurred after a few hours. Digitalis therapy was instituted.

Some days later the patient was able to breathe for six to seven hours without a respirator but she was evidently overstrained, sweated, and had an

elevated pulse rate. In view of the myocarditis, artificial respiration was continued for a further week. After three weeks spontaneous swallowing was possible, and the Rüsch tube was replaced by a silver cannula and use of the respirator discontinued.

Here, then, is a case of Guillain-Barré syndrome with pharyngeal and respiratory paralysis and the symptomatology and course typical of this syndrome. Samples of the spinal fluid were not obtained in the acute stage, but later a specimen contained 600 mg. per 100 cc. of protein without cells.

When admitted to hospital, the patient showed severe respiratory paralysis with hypoventilation, caused partly by atelectasis of the right lung, and manifest circulatory insufficiency, with weak, rapid pulse and peripheral coldness. The initial measure was to bring about free air passages by clearing the bronchi, via tracheotomy and bronchoscopy, then preventing further aspiration by intubation with the Rüsch tube. To secure free air passages in the further course, repeated removal of persisting secretion was required. The second measure was to ensure adequate ventilation. This was done for the first hour by means of a manual absorber unit for intratracheal positive pressure breathing, but thereafter ventilation was taken over by the new Engström respirator. A very important consideration was that spontaneous breathing, when it commenced to return, could proceed independently of the respirator, thanks to the extra inspiratory valve; and the patient was spared the distress caused by inability to breathe spontaneously in a closed system.

The symptoms of tachycardia and the electrocardiographic findings, pointing to severe acute myocarditis, are specially worthy of note. The severe initial hypoxia may conceivably have caused, or at all events largely contributed to, the acute myocarditis. From the cardiac point of view it is important that the artificial ventilation be adequate and not have an unfavorable influence on the venous return.

The practical measures in a case with progressive paralysis should be directed to the two main problems of free air passages and adequate ventilation. It is important that tracheotomy and intubation be done in pharyngeal paralysis as soon as progression to respiratory paralysis occurs. The risk of aspiration and atelectasis is always imminent, so that tracheotomy should not be delayed. The ventilatory state must be carefully checked, with repeated determinations of vital capacity and analysis of the blood gases.[10] The respiratory failure should be corrected in good time, before the patient gets into a poor condition with circulatory insufficiency. The method of artificial respiration depends on the degree of respiratory failure and the patient's ability to swallow. To ensure adequate ventilation in the severe acute cases in poor condition, endotracheal intermittent insufflation by the Engström respirator is to be recommended as a reliable method. Especially in cases with myocarditis and tachycardia, it is very important that adequate artificial ventilation be given early to prevent further damage to the heart.

Attempts to compensate ventilatory insufficiency by administration of oxygen alone are inadequate and may easily mask a dangerous carbon dioxide retention.

Patients with acute Guillain-Barré syndrome attended by pharyngeal and respiratory failure probably have a good chance of surviving, if treated on the foregoing principles. The prognosis quoad vitam should be equally as good as the prognosis with regard to restitution of the paralysis.

SUMMARY

The mortality in acute Guillain-Barré syndrome is high, 15% to 75% in undifferentiated series from the literature. In a series from the Stockholm Hospital for Infectious Diseases, comprising 15 cases with pharyngeal and respiratory paralysis, the total mortality was 47%. The mortality in the cases treated with artificial respiration by cuirass respirator was 100%.

This high mortality could probably be reduced if adequate measures were taken to ensure free air passages by early tracheotomy and intubation and to provide adequate artificial respiration by direct endotracheal intermittent insufflation.

A new respirator has been designed at the Stockholm Hospital for Infectious Diseases which provides endotracheal insufflation-inspiration and negative-phase expiration. It has proved most satisfactory in treatment of severe respiratory cases in the acute stage. A case of acute Guillain-Barré syndrome with pharyngeal and respiratory failure was successfully treated with the respirator.

The cardiocirculatory complex with tachycardia and acute myocarditis in the Guillain-Barré syndrome may lead to acute cardiac insufficiency and pulmonary edema. It is of great importance that these severe cases of the acute syndrome be given, at an early stage, adequate artificial ventilation with a reliable method.

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INVESTIGATION OF THE VALIDITY OF HALSTEAD'S MEASURES OF BIOLOGICAL INTELLIGENCE

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> The whole theory of learning and intelligence is in confusion. We know at present nothing of the organic basis of these functions and little enough of either the variety or uniformities of their expression in behavior. The concepts are so poorly defined that it has not been possible even to imagine a program of physiological research which seemed likely to reveal more than superficial relationships.[1]

SINCE Lashley wrote these words, in 1929, a large-scale attack, sponsored primarily by psychologists, has been directed toward elucidation of the learning process,[2] and a tremendous amount of time and energy has gone into the construction and standardization of formal scales of psychometric intelligence.* The "organic basis of these functions" in human beings, however, remains nearly as unclear as before.

A number of investigators have attempted to devise special tests for studying relationships between brain functions and behavioral potentialities.† Most of these researchers have recognized the value of objective and standardized test situations which yield quantitative results, not only as a basis for comparable general use of their tests, but also to permit replication and possible verification of the findings. Objective and reliable measurement has long been viewed as a fundamental tenet of science.

Independent evaluation of the validity of most of these testing procedures, unfortunately, has generally produced equivocal conclusions. The most likely explanation of this is that the original investigator's samples of subjects differed in certain unknown but relevant ways from the samples used in subsequent studies, even though brain damage may have been present in appropriate groups in each study. This is not surprising, of course, since it is usually impossible for a researcher to know completely all the variables pertinent to his measurements. The problem of controlling the influence of irrelevant variables through experimental design or methodological techniques would be theoretically possible, although likely very difficult, provided they had been identified. In addition, technical problems in measurement, such as the reliability of measures and equivalence of scaling units, add to the difficulties in experimental validation of original findings. Nevertheless, the search continues for behavioral tests selectively sensitive to the organic condition of the brain, because without such tests even partial fulfillment of the hope for elucidation of communicable relationships between brain function and behavior seems remote.

In 1947 Halstead [9] described and presented results for a battery of tests used with brain-damaged and control subjects. The results indicated that patients with predominantly frontal brain damage (unilateral or bilateral) did more poorly on most of the tests than did patients with nonfrontal damage. The group with nonfrontal damage, in turn, generally performed more poorly than the control group, composed of patients without brain damage. The results were very striking, mean intergroup differences in many instances being sufficiently large with relation to variability of the scores to have occurred less than 1 time in 1,000 on a chance basis. While it would seem highly unlikely that chance was responsible for the intergroup differences, the possibility remains that unknown factors differing sys-

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* References 3 and 4.

† References 5 through 12.

tematically between the groups may have been responsible, rather than brain damage. The present study is concerned with possible validation of Halstead's results, using the same tests administered in the same way, but with entirely different patients and in a different geographic locale.

MATERIAL AND METHODS

Fifty patients with proved brain damage or dysfunction composed one group. A second group consisted of 50 persons who had received neurological examinations before testing and showed no signs or symptoms of cerebral damage or dysfunction. Thorough histories relating to head injuries and diseases possibly involving the brain were obtained from each patient. None of the control subjects had positive anamnestic findings.

The patients in the two groups were individually matched on the basis of color and sex, and as closely as possible for chronological age and years of formal education. Means and standard deviations on the latter variables are presented in Table 1. Neither of the differences in central tendency or variability approached statistical significance. There were 35 men and 15 women in each group.

Each patient was interviewed before testing was begun. Only those were included in the study who were sufficiently alert and in contact with reality to provide detailed anamnestic information. None of the brain-damaged patients was acutely ill at the time of testing. Although many were examined postoperatively, testing was delayed until these patients had received maximal benefits from hospitalization and were ready for discharge. No attempt was made to control either the location or the extent of brain damage. The patients ranged from one having a surgical excision of a cortical tumor approximately the size of a thumbnail to a patient with complete agenesis of the corpus callosum. The diagnostic distribution of patients in each group is given in Table 2. It should be obvious from the types of brain damage that the results of this study will have no significance with respect to either location or extent of brain damage.

The inclusion of a substantial proportion of paraplegic and neurotic patients in the group without brain damage was done as a conservative procedure. Although several of the paraplegic patients had received traumatic spinal cord injuries, none had ever been unconscious from a head injury. The neurotic subjects were all sufficiently disturbed to be hospitalized for psychiatric treatment. These patients were included to minimize the possibility that differences in the test results for the brain-damaged and the control group could be attributed to hospitalization, chronic illness, and possible affective disturbances.

The Halstead battery of neuropsychologic measures was administered individually to each subject, in nearly all instances by a person other than myself. All tests were finally scored immediately after testing of each patient had been completed and before the groups were composed or the subjects matched on the controlled variables. Matching of

TABLE 1.—*Means and Standard Deviations for Chronological Age and Years of Formal Education for Groups With and Without Brain Damage*

	N	Mean Age, Yr.	S.D.	Mean Education	S.D.
Brain-damaged group	50	32.42	10.61	11.56	3.03
Non-brain-damaged group	50	32.36	10.78	11.58	2.85

TABLE 2.—*Diagnostic Distributions of Patients Included in Study*

Patients With Brain Damage		Patients Without Brain Damage	
Brain tumor	17	Paraplegia	13
Epilepsy	6	Depression	17
Closed head injury	6	Acute anxiety state	6
Penetrating head injury	6	Obsessive-compulsive neurosis	2
Cerebral vascular accident	4	Normal	12
Degenerative cerebrovascular disease	3		—
Cerebral atrophy	3		50
Cerebral abscess	2		
Subdural hematoma	1		
Dementia paralytica	1		
Developmental anomaly	1		
	50		

the subjects was done without reference to the variables which were to be compared. Intergroup statistical comparisons of mean differences were made on the 10 "discriminating" tests (those which Halstead proposed as being sensitive to the effects of frontal lobe damage). In addition, a graphic presentation of the difference scores on these tests was prepared.

RESULTS AND COMMENT

Mean scores on each test and the Halstead Impairment Index are presented graphically for each group in Chart 1. Before the intergroup comparisons are commented on, the design of the Chart should be explained. The norms for this profile chart were developed in Halstead's laboratory on the basis of a large group (N-451) composed of individually tested brain-damaged and control subjects. The heavy horizontal midline represents the criterion level for each test which Halstead found to differentiate best his control and frontal-brain-damaged subjects. A test performance above the criterion line indicates a performance similar to those characteristic of Halstead's subjects with frontal brain damage, and a score below is in the control range. Deciles above and below the criterion level are indicated along the vertical axis.

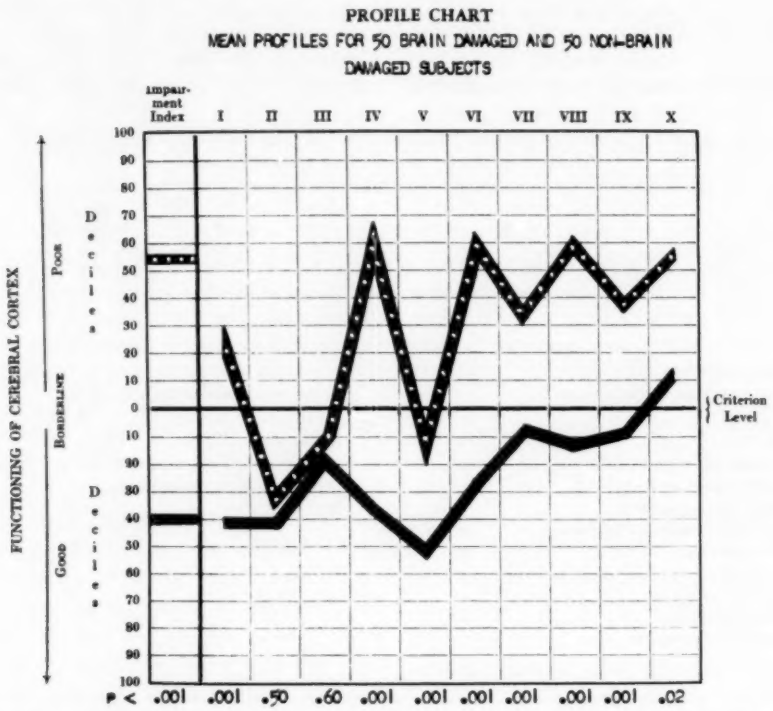

Chart 1.—Graphic presentation of mean values for matched brain-damaged and non-brain-damaged groups on Halstead's Impairment Index and 10 "discriminating" tests. *I*, Category Test; *II*, Critical Flicker Frequency; *III*, Critical Flicker Frequency—Deviation; *IV*, Tactual Performance Test—Time Component; *V*, Tactual Performance Test—Memory Component; *VI*, Tactual Performance Test—Localization Component; *VII*, Rhythm subtest—Seashore Tests of Musical Talent; *VIII*, Speech-sounds Perception Test; *IX*, Finger Oscillation Test; *X*, Time Sense Test—Memory Component.

Interpretation of the results in Chart 1 will be illustrated, using the Impairment Index as an example. The percentile rank of 56 on this variable for the brain-damaged group, above the criterion line, indicates that the mean score was at a level poorer than 56% of Halstead's patients who scored in the brain-damaged range on this variable.

The group without brain damage had a mean Impairment Index which was better than that obtained by 38% of Halstead's subjects who scored in the normal range.

In order that the meaning of these results may be understood with respect to the types of impairment which occur with brain damage, the tests should be described individually. A more detailed description of each test, together with its rationale, may be found in Halstead's book,[9] "Brain and Intelligence: A Quantitative Study of the Frontal Lobes." Significant mean differences were obtained with each measure except Tests II and III (Critical Flicker Frequency and Critical Flicker Frequency—Deviation).

The Impairment Index is a composite score based upon the 10 "discriminating" tests and is determined for an individual subject merely by counting the number of tests which fall above the criterion level. The mean difference between our brain-damaged and control groups was tremendous with relation to variability of differences. Statistical analysis indicated that chance alone could account for the difference in less than 1 in 10,000 repetitions of the experiment. These results indicate strongly that the Impairment Index measured a striking and consistent difference in our two groups.

The Category Test (Test I) utilizes a projection apparatus for presentation of stimulus material. The subject is required to "abstract" principles based upon variables such as size, shape, number, position, brightness, and color around which to organize his responses. Halstead's[9] factor analysis of his results, as well as a subjective interpretation, suggests that this test measures primarily abstraction ability. The nature of the problems posed seems to require the ability to group the stimulus material in accordance with proposed criteria, to recognize recurrent, and possibly significant, similarities in successive stimulus exposures in spite of the presence of pronounced dissimilarities, and to recognize the significance of stimulus details with relation to the overall pattern or principle that is being developed. The brain-damaged group was strikingly deficient in comparison with the control patients in these respects.

Tests IV, V, and VI represent various components of the Tactual Performance Test. This test utilizes a modification of the Seguin-Goddard form board. The subject is blindfolded and is not permitted to see the form board or blocks at any time. He first fits the blocks into their proper spaces with his preferred hand, then repeats the procedure with his other hand, and finally performs the task a third time using both hands. After the board and blocks have been put out of sight, the blindfold is removed and the subject is required to draw a diagram of the board representing the blocks in their proper spaces. The subject is scored for the total time needed to place the blocks (Test IV) and for the number of blocks correctly reproduced (Test V) and correctly localized (Test VI) in his drawing.

The Tactual Performance Test obviously requires coordination of tactile and kinesthetic cues with motor performance. No patients were included in this study who had any clinical evidence of dystereognosis. Further, the test would seem to be a measure to some extent of the ability of the patient to adapt satisfactorily to tactile and kinesthetic cues in a problem which would ordinarily be coordinated primarily by vision. The Memory Component (Test V) of this test is based upon the number of blocks correctly reproduced in the drawing of the board, and the Localization Component (Test VI), on the number correctly localized. Although the brain-damaged subjects required twice as much time to place the blocks, and thus were exposed to the board on the average twice as long as the controls, they were able to reproduce and localize significantly fewer of the shapes. While Tests V and VI are undoubtedly in part measures of incidental memory, Halstead's results suggest that they also are measures of abstraction ability. The brain-damaged patients apparently are impaired in the ability to relate the specific sensory cues they have obtained during the

course of placing the blocks to an over-all concept of the appearance of the board.

Test VII represents the Rhythm Subtest of the Seashore Tests of Musical Talent. Although this measure is roughly normally distributed in the general population, our brain-damaged subjects obtained poor scores with sufficient consistency to yield a highly significant mean difference in the group comparisons. They were regularly impaired in their ability to differentiate between pairs of rhythmic beats which were sometimes the same and sometimes different.

The patients with brain damage also performed more poorly than did the group without brain damage on the Speech-sounds Perception Test (Test VIII). This test consists of 60 spoken speech sounds, which are nonsense syllable variants of the *ee* digraph, presented in multiple choice form. The test is played from a tape record with the intensity of sound adjusted to the subject's preference. His task is to select the spoken syllable from the alternatives printed on his test form. The patients with brain damage made almost exactly twice as many errors as did the controls on this task, which requires perception and discrimination of auditory stimuli.

Test IX represents the Finger Oscillation Test, which is a measure of tapping speed, the subject using the index finger of the preferred hand. Although clinically significant ataxia or impairment of motor control of the upper extremities was not present in either group, the mean difference in favor of the group without brain damage was sufficiently large to have occurred considerably less than 1 time in 1,000 on a chance basis.

While significant statistically, the difference between the group with and the group without brain damage on Test X, the Time Sense Test—Memory Component, does not reach the extreme levels of confidence of the tests reported above. This test requires the subject to depress a key which permits a sweep hand to rotate on the face of a clock. The subject's task is to permit the hand to rotate 10 times and then to stop it as close to the starting position as possible. The Visual Component of this test is scored as the amount of error in 40 trials. The Memory Component is the error on 20 trials, interspersed among the visual trials in series of 10, when the face of the clock is turned away and the subject is asked to duplicate the visually controlled performance as closely as possible by memory. The mean error score of the brain-damaged subjects was nearly twice as great as that for the controls, but variability in both groups was great. Only on this test was the mean for the control group above the criterion level in Chart 1, although this level was approached in several other instances. This result is in accord with our deliberate attempt to include persons in the control group with recurrent hospitalizations, chronic illnesses, and neurotic disturbances.

Test II and III, Critical Flicker Frequency and Critical Flicker Frequency—Deviation, failed to differentiate between our group with and our group without brain damage. This result is consistent with Halstead's findings on patients with nonfrontal lesions, as compared with his control group. Although his results approached significance in the CFF comparison, the 0.05 probability level was not quite reached. Halstead did find that CFF was significantly lowered in his patients with frontal lobectomies, and the deviation on successive trials was also less in comparison with both the nonfrontal-brain-damaged and the control group. The types of brain damage included in the present study obviously do not permit any comment on Halstead's findings in his frontal lobectomy group. It should be noted, further, that the present results with CFF are not directly comparable, because of apparatus differences, to many of the reports which have appeared in the literature. An electronic instrument (Strobotac), with a short flash duration, housed in a specially constructed, soundproof apparatus, was used in this study. The instrument and testing conditions were strictly comparable to those used by Halstead.

A procedure for graphic comparison of the efficacy of these tests in differentiating

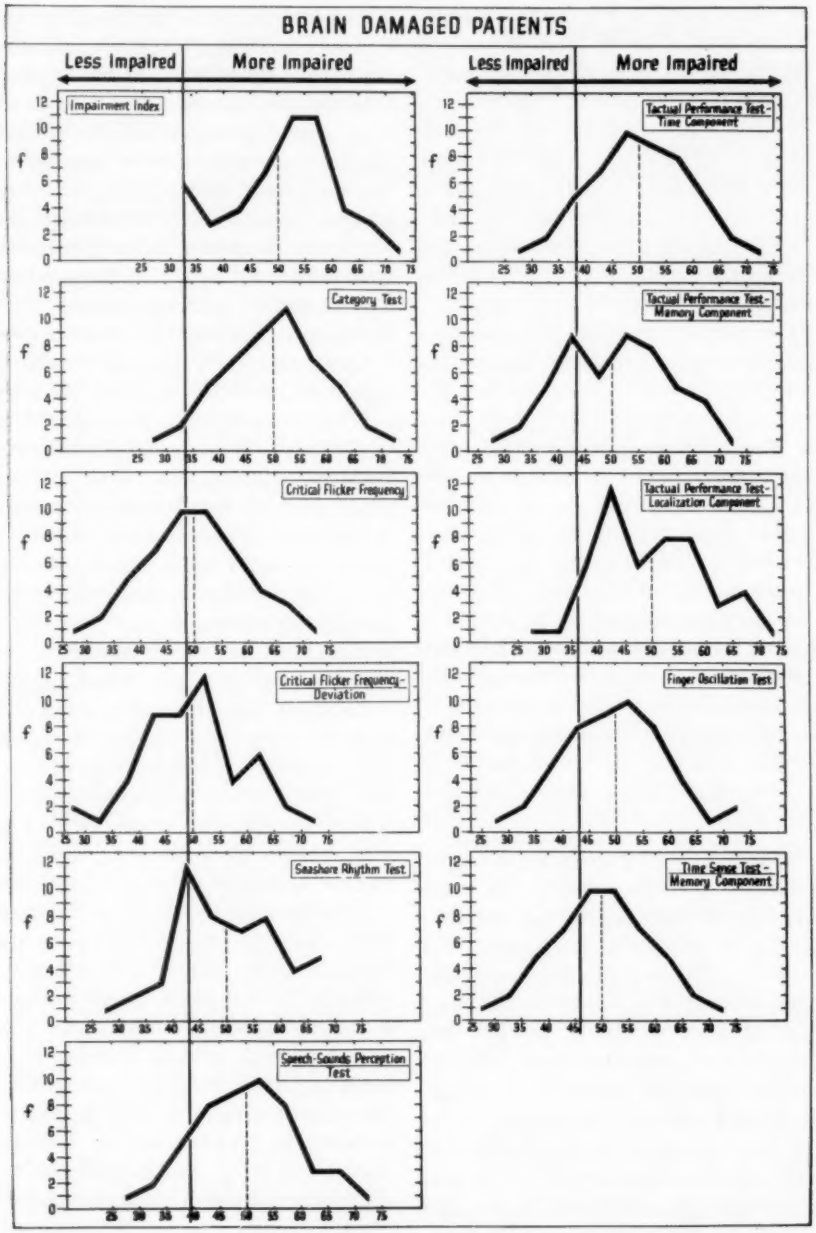

Chart 2.—Graphic comparison of efficacy of Halstead's tests in differentiating paired patients with and without brain damage. Area to right of continuous vertical line indicates brain-damaged patients who performed more poorly than did paired patients without brain damage. Raw difference scores for each variable were converted to a *T*-score distribution having a mean of 50 and a standard deviation of 10.

the patients with and without brain damage was worked out, and the results are presented in Chart 2. The frequency distribution for each test is based upon difference scores for the 50 paired brain-damaged and control subjects. To permit direct comparison of frequency distributions, the difference scores for each test were converted to *T*-scores, which have a mean of 50 and a standard deviation of 10. Further, the location of each frequency distribution on the horizontal axis is determined by the position in the distribution of the difference score of zero, or the point at which no difference was present in the scores of matched brain-damaged and control pairs. This point is indicated by the heavy vertical line which runs through the various distributions. The scales are so arranged that scores to the right of this line indicate brain-damaged subjects who have done more poorly than their matched controls. Scores to the left of the line indicate, on the contrary, deviations from the expected finding, or instances in which the control subject of the pair has done more poorly. The differentiating ability of any of the measures is thus apparent at a glance by comparing the areas under the curve to the right and the left of the zero, or "no difference" point (heavy vertical line).

The curve for the Impairment Index indicates that not a single patient with brain damage did better than his matched control, although there were six pairs who did equally as well. The quantitative magnitude of the Impairment Index would have permitted classification of the 50 pairs of patients into their diagnostic categories (brain-damaged or control) without a single reversal, leaving six pairs unclassified. The Category Test, which is principally a measure of abstraction ability, does nearly as well in differentiating the pairs according to diagnosis. With this test there were only three reversals, and these were of relatively small magnitude. While the mean differences were highly significant on the remaining tests, with the exception of the two measures based on flicker fusion, it is apparent from Chart 2 that they do not approach as closely a perfect job of classification as do the Impairment Index and the Category Test.

The results of this study indicate more consistent differences between the group with and the group without brain damage than were found generally by Halstead in his original comparison of nonfrontal-brain-damaged and control groups. Halstead's patients with frontal lobectomies generally performed as poorly as, or somewhat more poorly than did our brain-damaged patients. The magnitude and consistency of the differences in this validity study between the brain-damaged and the control patients constitute convincing evidence of the pertinence of results upon these tests to the organic condition of the brain. The results are particularly striking, for most attempts at verification of other testing procedures have resulted in equivocal conclusions.

The Halstead Impairment Index appears to be almost specifically sensitive to brain damage. Although our patients were matched in pairs on the basis of color, sex, age, and education, the paired subjects certainly must have differed in many ways besides the presence or absence of brain damage. No attempt was made to hold constant such variables as occupation, socioeconomic status, psychometric intelligence, or personality factors. Nevertheless, in no instance was the aggregate influence of such variables of sufficient weight to cause the control to have a higher Impairment Index than the brain-damaged patient with whom he was paired. There is probably no other measure of the psychological effects of brain damage for which such striking evidence of validity could be cited. No direct conclusion can be drawn regarding the possible influence of variables such as occupation, socioeconomic status, and I. Q. on the test results, since these factors were not systematically varied; but the results suggest that their effect is negligible as compared with that of brain damage.

SUMMARY AND CONCLUSIONS

Fifty brain-damaged patients were individually matched on the basis of color, sex,

chronological age, and years of formal education with 50 patients having no neurologic or anamnestic evidence of brain damage or disease. Intergroup statistical comparisons were made of results on the Halstead Impairment Index and 10 "discriminating" tests. Each of these measures, except two based on critical flicker frequency, showed significant differences. The magnitude of the mean differences with relation to variability was even more striking than in Halstead's original report. On the Impairment Index, for example, not a single brain-damaged person did better than his matched control, although six pairs had equal scores. The Category Test differentiated the groups according to diagnosis nearly as well as did the Impairment Index.

Although further validity studies are necessary, the present results suggest that the Halstead battery is sufficiently sensitive to the effects of organic brain damage to provide an objective and quantitative basis for detailed study of relationships between brain function and behavior.

Mrs. Barbara Melberg assisted in the test administration and statistical analysis of the data.

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PATTERN FORMED AT UPPER CERVICAL SPINAL CORD LEVELS BY SENSORY FIBERS OF SPINAL AND CRANIAL NERVES

Relation of This Pattern to Associated Gray Matter

TRYPHENA HUMPHREY, M.D., Ph.D., Pittsburgh

RECENT studies of the spinal tract (or descending root) of the trigeminal nerve in human fetuses [1] have demonstrated that a considerable number of fibers from all three divisions of this nerve pass throughout the first cervical segment of the spinal cord at the age when the embryo first responds to exteroceptive stimulation in the circumoral region (7½ weeks of menstrual age *). Less than a week later (at just over 8 weeks of menstrual age; Humphrey,[5] Fig. 12) large numbers of fibers from all divisions of the spinal tract of the trigeminal, or fifth cranial, nerve (V) have been observed to terminate in the middle third of the second cervical segment. Although some fibers in the spinal tract of V have been traced as far as the upper levels of the fourth cervical segment at a later fetal age (8½ weeks; Humphrey[5]), the great majority of the trigeminal fibers which pass into the spinal cord terminate in the middle third of the second cervical segment both in older fetal stages † and in the adult.‡

The termination of maxillomandibular, as well as ophthalmic, fibers of the trigeminal nerve in relation with gray matter of the upper cervical spinal cord brings to our attention three points worthy of further comment: (1) the existence, in these upper cervical cord levels, of a sensory fiber pattern for the entire embryo; (2) the appearance of a primitive center of centralization in the upper cervical region of the spinal cord, and (3) the presence of the most caudal part of the nucleus of the spinal tract of the trigeminal nerve in the upper cervical spinal cord levels, where it is included customarily as part of the dorsal horn gray matter. The present paper is devoted to a consideration of these three points.

MATERIAL AND METHODS

The observations made in connection with this study have developed out of earlier work on the spinal tract of the trigeminal nerve in human fetuses.§ These studies on the spinal tract of V were based primarily on a series of human fetuses from 14 to 34.3 mm. in crown-rump length, or from 6½ to 9½ weeks of menstrual age. For details concerning the preparation of this material and the methods used in studying it, the earlier papers § should be consulted.

The fetal ages mentioned in the following account are menstrual ages as determined by Hooker ‖ in connection with his studies on human fetal activity. The fetuses used for this study were all serially sectioned in toto. Listed by the research collection number in the order of menstrual age and crown-rump length, in millimeters, they are as follows: Fetus 113, 14.0 mm., 6½ weeks; Fetus 93A, 20.7 mm., 7½ weeks; Fetus 12, 22.0 mm., 8— weeks; Fetus 131, 22.6 mm., 8— weeks; Fetus 33, 32.0 mm.,

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* References 2, 3, and 4.

† References 1 and 6.

‡ References 6 and 7.

§ References 1 and 5.

‖ References 3 and 4.

9+ weeks; Fetus 134, 34.3 mm., 9½ weeks. Fetuses 33, 93A, and 113 were stained by the activated Protargol (strong silver protein N. F.) method of Bodian [8]; all of the others are pyridine-silver preparations.

SENSORY FIBER PATTERN IN UPPER CERVICAL REGION OF SPINAL CORD

Up to the time that the human embryo first responds to exteroceptive stimulation,

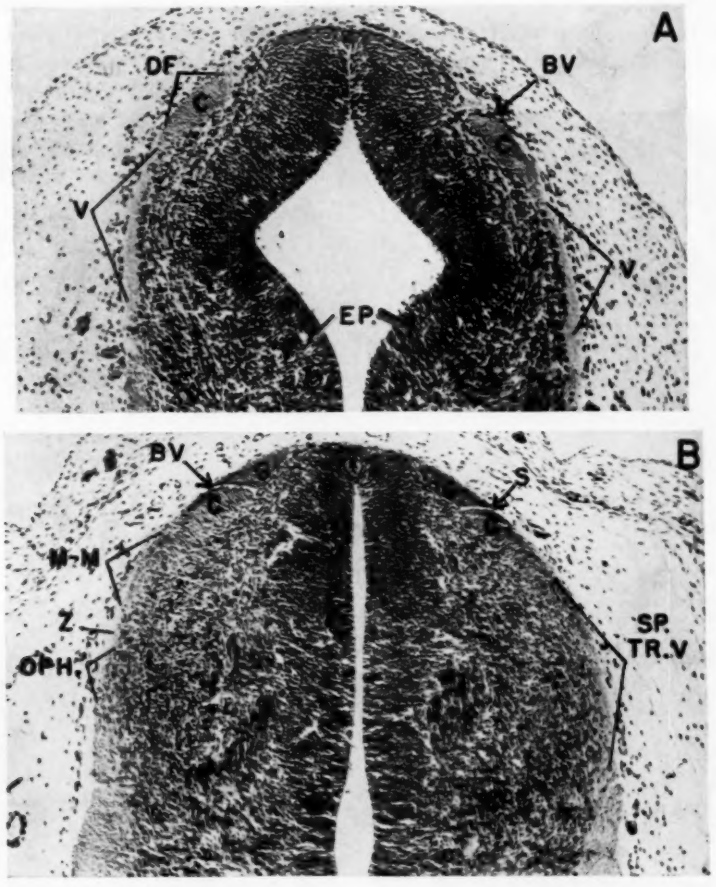

Fig. 1.—Photomicrographs of transverse sections of the spinal cord to show the development of the dorsal funiculus. Activated Protargol preparations according to the method of Bodian [8]; × 75.

BV, blood vessel in region of dorsal intermediate septum; *C*, fasciculus cuneatus; *DF*, dorsal funiculus; *EP.*, ependyma surrounding the central canal; *G*, fasciculus gracilis; *M-M*, maxillomandibular fibers of the spinal tract of the trigeminal nerve; *OPH.*, ophthalmic fibers of the spinal tract of V; *S*, region of dorsal intermediate septum; *SP.TR.V*, spinal tract of V; *V*, area occupied by the few scattered fibers found in the spinal tract of V at this age; *Z*, relatively fiber-free zone in spinal tract of V between the maxillomandibular fibers, dorsally, and the ophthalmic fibers, ventrally.

A, section through the dorsal part of the first cervical segment of the spinal cord of an embryo of 6½ weeks of menstrual age (No. 113, 14 mm. in length; section 8-3-5). Note that at this age no fibers of the dorsal funiculus have collected dorsomedial to the small blood vessel (*BV*) which marks the approximate location of the dorsal intermediate septum at later ages.

B, section through the dorsal portion of the first cervical segment of the spinal cord of an embryo at 7½ weeks of menstrual age (No. 93A, 20.7 mm. in length; section 93-1-8). It will be noted that an appreciable number of fibers have accumulated in the area allocated primarily to fasciculus gracilis, namely, the zone dorsomedial to a small blood vessel (or the tissue around it) frequently seen crossing the dorsal funiculus and lying, at the surface of the spinal cord, approximately at the border zone between the two fasciculi constituting the dorsal funiculus.

there is no indication that the dorsal funiculi at the first two cervical levels of the spinal cord (C1 and C2) contain fibers from caudal spinal cord levels (Fig. 1*A*). At 7½ weeks, however, an appreciable number of fibers of each dorsal funiculus are found medial to a blood vessel (Fig. 1*B*) which frequently marks the area of the dorsal intermediate septum in the fully developed spinal cord. In the adult, this septum reaches the surface of the dorsal funiculus near the boundary between fasciculus gracilis (column of Goll) and fasciculus cuneatus (column of Burdach), although deeper in the dorsal funiculus the septum does not follow the pattern demonstrated for the fibers from different

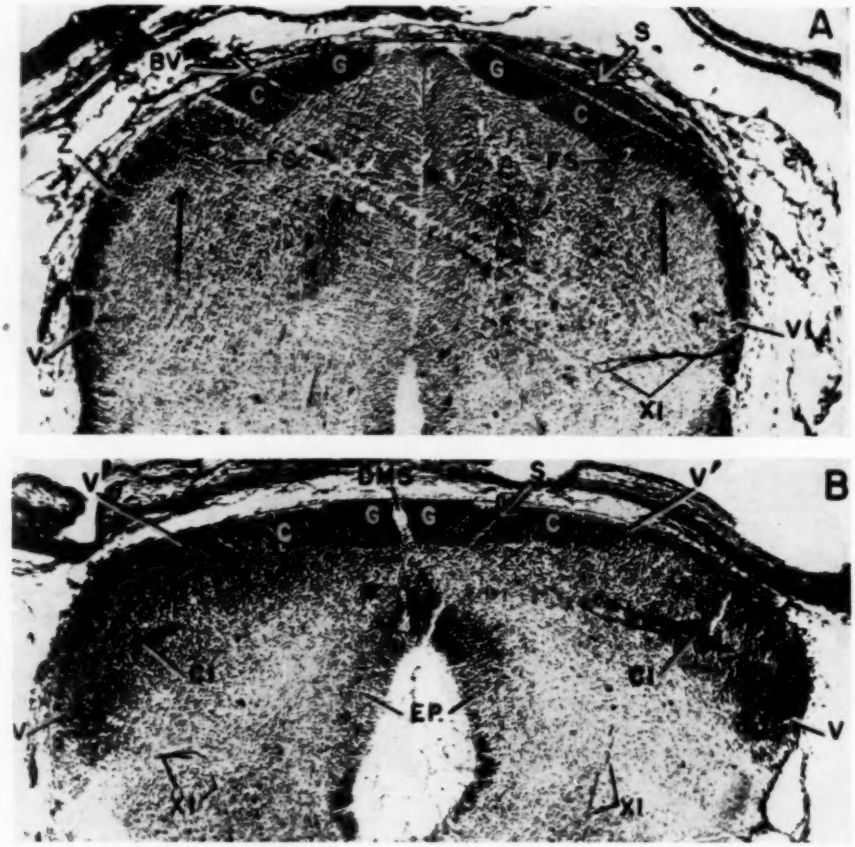

Fig. 2.—Photomicrographs of transverse sections of the spinal cord to show fasciculus gracilis and fasciculus cuneatus. Pyridine-silver preparations. × 75.

BV, blood vessel at tip of arrow, marking area of dorsal intermediate septum at the surface of the spinal cord; *C*, fasciculus cuneatus; *CI*, dorsal roots of first cervical nerve; *DMS*, dorsomedian septum; *EP*., ependyma; *FS*, fasciculus solitarius; *G*, fasciculus gracilis; *S*, dorsal intermediate septum at tip of arrow; *V* and *V'*; ventral and dorsal borders, respectively, of the spinal tract of V; *XI*, rootlets of spinal accessory nerve; *Z*, relatively fiber-free zone marking the border between the maxillo-mandibular division of V, dorsally, and the ophthalmic fibers of V, ventrally.

A, section through the dorsal part of the first cervical segment of the spinal cord of an 8½-week fetus (No. 19, 26.5 mm. in crown-rump length; section 17-1-8). A continuation dorsalward of the lines indicated by the arrows would pass through the region where the spinal tract of V borders on fasciculus cuneatus.

B, section through the dorsal portion of the first cervical segment of the spinal cord of a 9½-week fetus (No. 134, 34.3 mm. in crown-rump length; section 54-2-3).

body segments.¶ It may be assumed, then, that some fibers from the sensory roots of those caudal spinal nerves which constitute fasciculus gracilis have grown cephalad into C2 and C1 as early as 7½ weeks of menstrual age. Inasmuch as only part of the exteroceptive fibers in fasciculus gracilis are believed to pass all of the way from caudal levels of the spinal cord to nucleus gracilis,[11] it is possible that some of the fibers present in this area of the dorsal funiculus at cervical levels in early fetal life originate in gray matter of the spinal cord and represent part of a relay system from caudally situated spinal ganglia.

A variation in the staining reaction of the fibers forming the dorsal funiculus differentiates the border area between fasciculus gracilis and fasciculus cuneatus in the 8½-week human fetus (Fig. 2*A*). As would be expected, this boundary does not entirely correspond to the dorsal intermediate septum, which consists of a readily identifiable linear zone with few fibers, which often contains a blood vessel (Fig. 2*A*). On the contrary, the boundary often crosses this septum, as does the pattern of sensory nerve fibers shown by Foerster.[10]

At 9½ weeks the dorsal intermediate septum may likewise cross the border between fasciculus gracilis and fasciculus cuneatus or lie entirely lateral to it (Fig. 2*B*), as is often true earlier (Fig. 2*A*). By this age, however, the dorsal median septum is replacing the ependyma in the middorsal region of the spinal cord at upper cervical levels. Consequently, in transverse sections, fasciculus gracilis begins to approach its adult spinal cord relations, as to both its position along the dorsal median septum and its triangular outline in transverse sections (Figs. 2*B* and 5*B* and *C*). At the age at which fasciculus gracilis can first be identified at upper cervical levels, however, its fibers lie somewhat more dorsal to those of fasciculus cuneatus than medial to them (Fig. 1*B*), and this relationship is retained to a certain extent at 8½ weeks (Fig. 2*A*).

As soon as the fibers of fasciculus gracilis, fasciculus cuneatus, and all three divisions of the spinal tract of V grow into the first and second cervical spinal cord segments, a complete exteroceptive sensory pattern, representing both the body and the face, is established at these levels by the entering sensory root fibers (or primary sensory fibers). This pattern of sensory fibers is in the transverse plane of the central nervous system, with the arrangement such that the lowest sacral levels are represented most dorsomedially[9] and the ophthalmic distribution of V most ventrolaterally (Fig. 3).

It is suggested that, during the early period of fetal activity (up to 9½ weeks, when the earliest localized reaction has been noted in response to stimulation of the trigeminal nerve[4]), the fibers which constitute this complete exteroceptive sensory pattern are

¶ References 9 and 10.

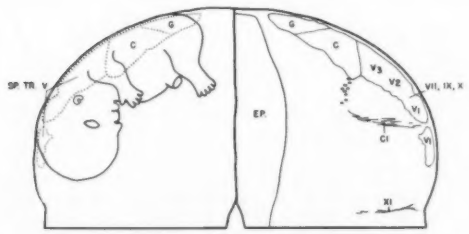

Fig. 3.—A drawing of the dorsal half of a transverse section of the spinal cord of an 8½-week human fetus (No. 19, 26.5 mm. in crown-rump length) at the level of upper C1. The outline of the spinal cord and the tracts shown were drawn by projecting the section on a ground glass screen at the appropriate magnification.

On the left side of the section the outline of the body and head of an 8½-week fetus has been superimposed over the spinal tract of V and the dorsal funiculus. Note that the proportionately large area supplied by the trigeminal nerve of the fetus at this age is in harmony with the large spinal tract of V. Similarly, the relatively small lower extremities and lower trunk are in accord with the poorly developed fasciculus gracilis at this age.

C, fasciculus cuneatus; *C1*, sensory rootlets of first cervical nerve; *EP.*, ependyma; *G*, fasciculus gracilis; *SP. TR. V*, spinal tract of the trigeminal nerve; V_1, V_2, V_3, ophthalmic, maxillary, and mandibular divisions of the spinal tract of V; *VII, IX, X*, area of the spinal tract of V which has been suggested[1] as the site of the cutaneous sensory fibers of the facial, glossopharyngeal, and facial nerves; *XI*, rootlets of the spinal accessory nerve. The small circles between the ventral tip of the fasciculus cuneatus and the sensory rootlets of C1 represent the fasciculus solitarius.

concerned with the transmission of impulses of general sensation or crude touch, probably primarily of a noxireceptive type (Sherrington [12]), rather than either pain or a more specialized type of tactile sensitivity. That these fibers are not the pain-carrying fibers of the adult spinal nerves is indicated by the fact that the pain fibers retain their primitive segmental distribution within the spinal cord even in adult man and do not ascend more than a segment above their level of entrance.# Consequently, only the pain fibers from the highest cervical levels and those in the spinal tract of V could be represented. The fact that no specialized sensory receptors of exteroceptive type have been demonstrated for human fetuses during this early period of fetal activity indicates that no discriminatory sensations can be represented at this time. Indeed, Hogg [13] found no specialized receptors until 12 weeks of menstrual age, when only early indications of Merkel's tactile end-discs were identified, in the form of nerve fibers in contact with the basal cells of the epithelium (Hooker and Humphrey [14]). Consequently, a general type of sensation, probably primarily of a noxireceptive nature, is undoubtedly the feeling most frequently aroused on stimulation of the naked nerve fiber tips present under the epithelium at earlier ages, although, according to Ariëns Kappers,[11] stimuli of agreeable nature may also be received by such fibers.

Inasmuch as proprioceptive fibers are present in fasciculus gracilis and fasciculus cuneatus and, according to Thelander [15] and Szentagothai,[16] some proprioceptive fibers of the mesencephalic root of V may pass into the uppermost spinal cord levels as well, the fiber pattern at these levels may include proprioception. Like the exteroceptive sensations during early fetal life, however, proprioception must be of a crude or primitive type, such as is evidently present in lower vertebrates (Ariëns Kappers and associates [11]), for no specialized proprioceptive receptors have been demonstrated in human fetal muscles until the age of 11 weeks. In 11-week fetuses, however, Cuajunco [17] found "characteristic nerve endings" present "around one or more myoblasts" in the biceps brachii,* and it seems probable that such receptors are to be found in the axial muscles of the neck region even earlier.

The spinal tract of V is large, as compared with the dorsal funiculus (fasciculus gracilis and fasciculus cuneatus), when trigeminal stimulation first produces a response (Figs.

References 10 and 11.

* Cuajunco,[17] p. 125.

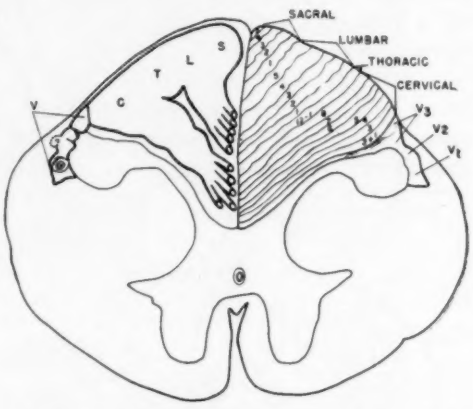

Fig. 4.—Drawing of a transverse section of the first cervical segment of the spinal cord of adult man. On the right side of the figure the areas of the dorsal funiculus allocated to fibers of the different spinal nerves are shown in accordance with the designation of Foerster.[10] The position of the fibers of the spinal tract of V follows that given by Riley [25] for the first cervical segment of the spinal cord. The general location of the mandibular, maxillary, and ophthalmic fibers of V in its spinal tract is the one customarily given (Humphrey, References 1 and 5).

On the left side of this figure, a homunculus of adult man has been superimposed upon the area occupied by the dorsal funiculus and the spinal tract of the trigeminal nerve to show that, in the first cervical segment of the adult spinal cord, as well as in the fetus, a complete pattern of exteroceptive sensory nature for face and body is formed by the incoming cutaneous sensory root fibers of spinal and cranial nerves. Note that in the adult the dorsal funiculus is large as compared with the spinal tract of V, just as the surface of the trunk and extremities, supplied by spinal nerves, is large in comparison with the cutaneous areas of the face supplied by the fibers of cranial nerves.

C, T, L, S, cervical, thoracic, lumbar, and sacral areas of the dorsal funiculus; *V,* facial areas supplied by the trigeminal nerve and the cutaneous sensory fibers of VII, IX, and X; V_1, V_2, V_3, ophthalmic, maxillary, and mandibular divisions of the spinal tract of the trigeminal nerve, respectively.

1*B*, 2, and 3). In this respect, it should not be forgotten that the dorsal funiculus contains many proprioceptive fibers, as well as those of exteroceptive type, whereas exteroceptive fibers are the sole recognized constituent of the spinal tract of the trigeminal nerve. Consequently, the spinal tract of V is still larger, proportionally, when compared with only the exteroceptive components of fasciculus gracilis and fasciculus cuneatus. It is obvious, then, that in the fetus the large spinal tract of V and the comparatively small dorsal funiculus are in harmony with the large cutaneous sensory area supplied by V and the relatively small trunk of the fetus itself at this time (Fig. 3). The proportionately large size of the spinal tract of V is also in harmony with the functional status of the fetus, for, up to 10 to 10½ weeks at least, the only cutaneous areas known to be sensitive to stimulation are those supplied by the trigeminal nerve.[4] To a certain extent in later fetal life, when the cutaneous areas innervated by spinal nerves become responsive to stimulation, and markedly in the adult, the situation is reversed. For, in the adult (Fig. 4), although the same exteroceptive sensory pattern is present in the upper cervical region of the spinal cord, the dorsal funiculus is large as compared with the spinal tract of V, just as the cutaneous surfaces supplied by spinal nerves in the adult are very extensive as compared with those supplied by the trigeminal nerve.

PRIMITIVE CENTER OF CENTRALIZATION

In 1909 Coghill † (Herrick ‡) suggested that the area of "most primitive centralization of the nervous system . . . would seem to be in close relation to the cephalic musculature of the trunk" and the neurons innervating it, and, further, that the "most primitive, diffuse exteroceptive" sensory system would be involved. Coghill also indicated that this center of control would be located in "the region corresponding to" the lower portion of the medulla or the upper part of the spinal cord. Additional details as to the structures constituting such a center of centralization of the nervous system were not given by Coghill.

It is suggested that the exteroceptive sensory fiber pattern just described for the human embryo, together with the associated gray matter at upper cervical spinal cord levels, constitutes the morphologic basis for such a primitive center of centralization (or integration) as was referred to by Coghill.[18] Thus, incoming sensory root fibers related to nondiscriminatory exteroceptive sensations from all regions of the body, as well as the face, are arranged, in this region, to form a pattern of body and face (Fig. 3). Inasmuch as these fibers will distribute impulses to the underlying gray matter in accordance with their location in this fiber pattern, that is, from ventrolateral to dorsomedial in the transverse plane of the embryonic central nervous system, a similar pattern must be present on the underlying gray matter in the upper cervical levels of the spinal cord. Consequently, the concentration of incoming exteroceptive sensory impulses related primarily to the transmission of noxireceptive stimuli from all cutaneous surfaces of the embryo would point to the area of their termination as the center of "most primitive centralization" (or integration) to which Coghill [18] made reference.

Although constituting the most primitive center of centralization or integration in the central nervous system, the upper cervical spinal cord center resembles higher centers of centralization in many ways. For example, it is also characteristic of the more highly developed centers, such as the diencephalon and the cortex, that they receive sensory impulses from all regions of the body. In addition, however, these higher centers receive stimuli covering a wide range of sensory modalities. In this regard, also, the cervical cord region of centralization resembles the higher centers, although the number of modalities represented is more limited. Thus, though the cervical cord center probably relates the organism primarily to its external

† Coghill,[18] p. 101.

‡ Herrick,[19] p. 89.

environment through the cutaneous exteroceptive sensory field, the center must also receive some proprioceptive impulses from both body and head regions, as was pointed out earlier (p. 40). In addition, the center will also receive general visceral afferent stimuli from the fibers of fasciculus solitarius. Indeed, this tract has been identified in the first cervical segment of the spinal cord in human embryos only 12 mm. in length by Wilson, Windle, and Fitzgerald [20] and is readily seen in both the first and the second cervical segment at 22 mm. (8 weeks of menstrual age; Humphrey,[5] Figs. 8 and 9) and 26.5 mm. (8½ weeks; Figs. 2*A* and 3).

In contrast to the pattern of primary exteroceptive sensory fibers and the associated gray matter in the transverse plane at upper cervical spinal cord levels is the pattern of primary motor neurons along the longitudinal axis of the central nervous system, with the oculomotor nucleus and nerve farthest cephalad and the fifth sacral and coccygeal neurons and motor roots most caudalward. Motor activity, therefore, may occur anywhere along this longitudinally distributed pattern of primary (or lower) motor neurons. The specific reaction which follows stimulation, then, is often dependent upon integration of stimuli in some center of centralization.

From the upper cervical spinal cord center of integration, probably only axial flexion, as observed in fetal activity studies in response to perioral stimulation of the trigeminal receptors (Hooker §), is produced. Initially this movement is limited to the neck region alone and is most frequently, although not always, contralateral to the side stimulated. In other words, the earliest fetal response to exteroceptive stimulation of the face is carried out over the motor neurons located in the upper cervical region of the spinal cord, at the level of the primitive center of centralization under consideration. This most primitive center, then, relates the organism primarily to the external environment, so that potentially noxious external stimuli ‖ produce an avoiding reaction,¶ that is, axial flexion contralateral to the side of stimulation.

No contralateral axial flexion response, or avoiding reaction, has been noted for human or other mammalian embryos on stimulation of caudal areas of the body,[3] as might be expected if fibers of fasciculus gracilis reach this primitive centralization center in the upper cervical levels of the spinal cord relatively early in development. Likewise, stimulation of caudal regions of the body did not produce trunk movements in most of the amphibian larvae studied by Coghill.[24] For one tailed amphibian (Diemyctylus torosus), however, Coghill [18] observed a reaction to stimulation in the tail region. For this urodele amphibian, contralateral (and sometimes ipsilateral) axial flexion in the cervical region was seen repeatedly by Coghill [18] in response to stimulation of caudal cutaneous areas, as well as after touching skin surfaces supplied by cranial nerves V and X.

Although the cervical spinal cord center of centralization may receive some proprioceptive, visceral afferent, and perhaps even other sensory, modalities (p. 41), this center is evidently dominated by impulses of exteroceptive type which result in contralateral flexion of the body or, more rarely, in ipsilateral flexion. Moreover, in the exteroceptive field, impulses brought in over the trigeminal nerve appear to determine or regulate the response produced. Inasmuch as the cutaneous areas supplied by the trigeminal nerve are the earliest of all skin surfaces to respond to stimulation (beginning at 7½ weeks, Hooker #), this is to be expected. Furthermore, the trigeminal nerve provides the only functioning exteroceptive sensory fibers during the first two and a half to three weeks of fetal activity (between 7½ and 10 to 10½ weeks of menstrual age, Hooker [4]). Consequently, when spinal nerves become sensitive to exteroceptive stimuli, i. e., when

§ References 3 and 4.

‖ References 11, 12, 14, and 23.

¶ References 5, 14, 21, and 22.

References 3 and 4.

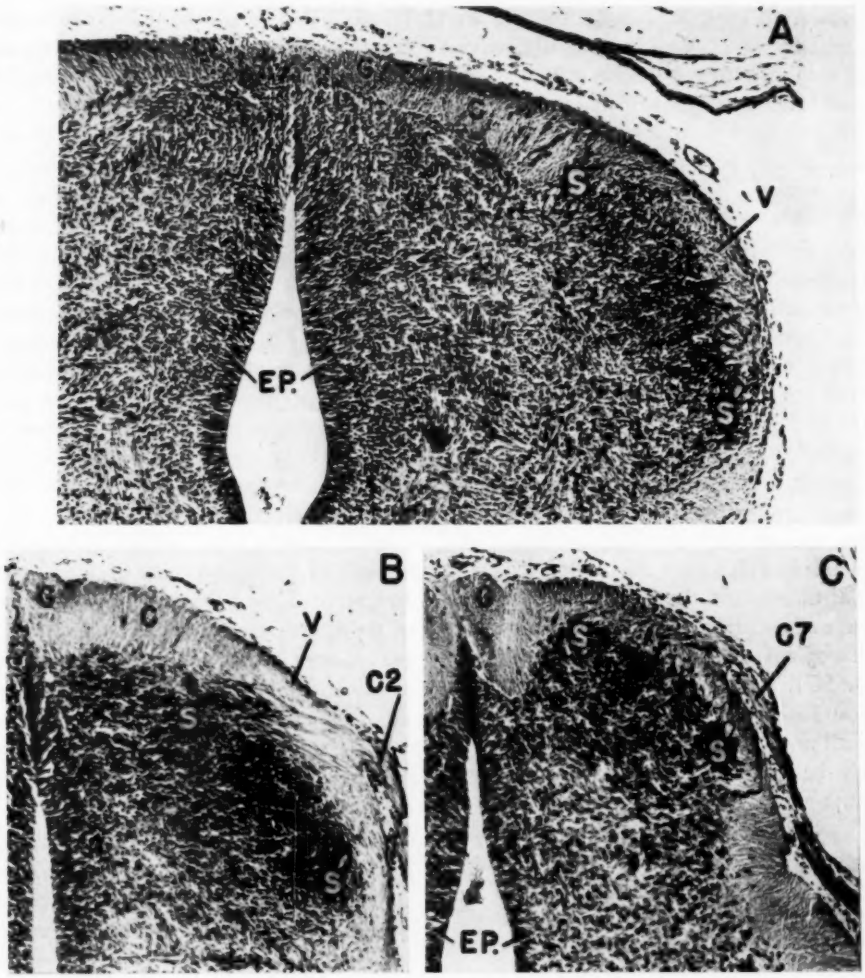

Fig. 5.—Photomicrographs of transverse sections of the dorsal horn region of the spinal cord of a 9-week human fetus (No. 33, 32 mm. in crown-rump length) to show the relative size of the substantia gelatinosa of the dorsal horn at the levels of C1, lower C2, and C7. Activated Protargol preparation according to the method of Bodian [8]; × 75.

C, fasciculus cuneatus; *C2*, dorsal roots of second cervical nerve; *C7*, dorsal roots of seventh cervical nerve; *EP.*, ependyma; *G*, fasciculus gracilis; *S* and *S'*, dorsomedial and ventrolateral regions, respectively, of the substantia gelatinosa portion of the dorsal horn; *V*, spinal tract of the trigeminal nerve.

A, section (No. 54-3-2) through the middle of the first cervical segment where the substantia gelatinosa is great in amount, although the first cervical sensory rootlets are usually absent. It is suggested that here the greater part of the substantia gelatinosa and underlying gray matter constitutes the most caudal part of the subnucleus caudalis portion (Crosby and Yoss [23]; nucleus caudalis of Olschewski [26]) of the nucleus of the spinal tract of V.

B, section (No. 59-3-4) through the caudal third of the second cervical spinal cord segment, where only a few fibers of the spinal tract of V have been shown to terminate and the substantia gelatinosa of the dorsal horn area is much reduced in size as compared with that in C1.

C, section (No. 75-1-5) through the middle of C7, where, in spite of the great number of exteroceptive sensory fibers from the extremity, the substantia gelatinosa of the dorsal horn is small as compared with its size in C1 (and upper C2), where many fibers of the spinal tract of V have been shown to terminate.

stimulation of the palm of the hand first produces finger flexion (at 10 to 10½ weeks, Hooker [4]), the finger flexion reflex is suppressed or inhibited if ipsilateral maxillomandibular and palmar areas are touched simultaneously with a hair.*

CERVICAL CORD PORTION OF NUCLEUS OF SPINAL TRACT OF FIFTH CRANIAL NERVE

The termination of large numbers of fibers of the spinal tract of V in the region of the dorsal horn gray matter † at upper cervical segments of the spinal cord indicates that part of the dorsal horn at these levels is, in reality, the caudal end of the nucleus of the spinal tract of V.[1] This interpretation is supported by the fact that the substantia gelatinosa is clearly larger in C1 (Fig. 5*A*), where the sensory rootlets are small and often absent (Humphrey [5]), and in the upper part of C2, than in the cervical enlargement, where many exteroceptive sensory fibers enter the spinal cord from the upper extremity (Fig. 5*C*). In the caudal part of C2 (Fig. 5*B*) and in C3, where the spinal tract of V is small and the neurons related to its fibers should be correspondingly reduced in number, the gray matter at the tip of the dorsal horn, which, as a whole, receives pain and temperature impulses over both cervical and trigeminal nerves, is also decreased in size as compared with the area it occupies in C1. The large size of the substantia gelatinosa in C1 in the adult is equally evident on comparing this level ‡ with a level through the cervical enlargement, such as that for C7§ or with one where the spinal tract of V is small, such as the level of C3.‖

In C1 and upper C2, where the substantia gelatinosa is large in amount as compared with more caudal levels, this gelatinous substance extends far dorsomedially along the dorsal horn in the adult. Caudal to the termination of the spinal tract of V, the substantia gelatinosa lacks this dorsomedial extension. It is this dorsomedial area of the dorsal horn which Crosby and Yoss [23] have included in their subnucleus caudalis of the nucleus of the spinal tract of V in various lower vertebrates.

Inasmuch as a considerable portion of the dorsal horn gray matter in C1 and upper C2 (and a smaller amount in caudal C2 and in C3 as well) is associated with the spinal tract of V, these neurons should be considered as constituting a cervical cord portion of the subnucleus caudalis subdivision (Crosby and Yoss [23]) of the nucleus of the spinal tract of V of man, as well as of lower vertebrates. This cervical cord region, then, should be added to the most caudal part of Olszewski's [26] nucleus caudalis portion (nucleus tractus spinalis trigeminalis caudalis) of the nucleus of the spinal tract of V in macaque and man. This overlapping of the nucleus of the spinal tract of V with the spinal cord gray matter associated with the dorsal roots of spinal nerves is not mentioned by Olszewski, although he states that his nucleus caudalis is continuous with the dorsal horn of the spinal cord and emphasizes the similarities between the dorsal horn and the nucleus caudalis portion of the nucleus of the spinal tract of V. It is this subnucleus caudalis (Crosby and Yoss [23]; nucleus caudalis of Olszewski [26]) portion of the nucleus of the spinal tract of V, including the region within the spinal cord itself, which appears earliest phylogenetically (Crosby and Yoss [23]).

CONCLUSIONS

As early as the human embryo is able to respond to stimulation of the circumoral distribution of the trigeminal nerve, fibers of the fasciculus gracilis, as well as those of the fasciculus cuneatus and the spinal tract of the trigeminal nerve, have reached the highest cervical levels of the spinal cord. Here the primary exteroceptive sensory fibers of cranial and spinal nerves form a complete pattern related to general or crude tactile sensibility for body and face (in C1 and upper C2), beginning as soon as the fasciculus

* References 4 and 14.

† References 1 and 5.

‡ Riley,[25] p. 40.

§ Riley,[25] p. 30.

‖ Riley,[25] p. 38.

gracilis is first represented (7½ weeks). Although the relative sizes of the dorsal funiculus and the spinal tract of V are reversed in the adult from their relation in the fetus, the fundamental relation of the fiber pattern remains the same in the adult.

The presence and the termination of fibers carrying exteroceptive sensations from all regions of the body and face, together with proprioceptive fibers (fasciculus gracilis, fasciculus cuneatus, and perhaps a few fibers of the mesencephalic root of V) and those of general visceral afferent nature (tractus solitarius), are indicative of the formation of a primitive center of centralization (see also Coghill [18]), or integration, in highest cervical spinal cord levels. It is the motor neurons in this region of centralization in the spinal cord which first respond to exteroceptive stimulation of the perioral region of the fetus by axial flexion contralateral to the site of stimulation, that is, an avoiding reaction of the organism as a whole.

Part of the dorsal horn gray matter in the upper cervical levels of the spinal cord, larger in amount in C1 and upper C2, constitutes a cervical cord portion of the nucleus of the spinal tract of V. This cervical cord region of the subnucleus caudalis (Crosby and Yoss[23]) of the nucleus of the spinal tract of V probably occupies the dorsomedial part of the dorsal horn at these levels. In lower C2, in C3, and in some cases in upper C4, a smaller part of the dorsal horn gray matter must also belong to this cervical cord portion of the nucleus of the spinal tract of V, for some trigeminal fibers of this tract have been found to terminate as far caudally as the upper levels of C4 (Humphrey [5]).

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RESPONSE OF BLOOD EOSINOPHILES AND PLASMA 17-HYDROXYCORTICOIDS TO INSULIN SHOCK THERAPY

Correlation with Clinical Effects

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INTRODUCTION

DEEP INSULIN shock therapy for schizophrenia affords an opportunity to study the effect of repeated acute stress in humans and to correlate the measured responses with improvement or nonimprovement of the schizophrenic condition. The effects of acute stress upon certain indices of adrenocortical activity have recently been critically reviewed by Thorn, Jenkins, and Laidlaw,[1] and factors controlling the concentration of blood eosinophiles, by Best and his collaborators.[2] The acute fall of eosinophiles resulting from large doses of insulin or from electroshock has been frequently observed. However, the effects of repeated acute stress, such as a course of insulin shock therapy upon the eosinophile count and other more direct measurements of adrenocortical activity have not been as thoroughly studied. Furthermore, the changes in the eosinophile count occurring throughout the course of insulin shock therapy are of considerable clinical interest because of the observations of Rud,[3] Altschule and associates,[4] and others of marked changes in the eosinophile count coincident with or prior to spontaneous improvement in major psychoses. For these reasons, we have studied in detail the blood eosinophile count before, throughout, and after completion of a course of deep insulin shock therapy in 35 patients and changes in plasma 17-hydroxycorticosteroid concentrations and eosinophiles in 3 additional patients.

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METHODS

A. Selection of Patients and Classification of Results.—Thirty men and 5 women with schizophrenia for whom insulin shock therapy had been recommended by the psychiatric staff were selected for detailed study of their eosinophile counts as outlined below, and an additional 3 men for study of plasma 17-hydroxycorticosteroid concentrations and eosinophiles at longer intervals. Five of the 35 had had a previous course of insulin shock therapy (the most recent being 16 months before present observations were made), and 17 of these patients had had one or more previous series of electroshock treatments. The average interval between clinical onset of mental illness and current treatment was 58 months, with a range of 4 to 135 months. The average age of the group was 30 years, with a range from 21 to 46 years. Table 1 summarizes certain pertinent clinical factors in the improved and unimproved groups.

Patients classified as improved showed beneficial changes in their psychiatric status at the termination of, or within one week following, completion of insulin shock therapy. The clinical conditions and results were rated independently by three psychiatrists. In all but two instances there was complete agreement as to diagnosis, and in all but two instances, complete agreement regarding presence of distinct improvement. It is emphasized that the purpose of this study was to attempt to correlate changes in the eosinophile levels with improvement in the psychiatric status at the time the counts were made, and not to determine the clinical value or prognostic implications of changes in the eosinophile count.

B. Insulin Shock Therapy (I. S. T.).—Insulin shock therapy was administered in courses of 10 or 12 weeks (six or five days a week, respectively) by a modification of the technique of Bond and Shurley.[5] The aim of this technique is to produce coma as early as possible in the course of insulin shock therapy through increasing the dose daily by geometric progression, i. e., 50, 100, 200, 400, and 800 units, then by increments of 200 units daily until coma is produced. Five units was given daily for a period of five days prior to instituting the course of I. S. T. The average initial coma dose was 1,080 units for the 30 men and 500 units for the 5 women, with a range of 200 to 1,800 and 90 to 800 units.

respectively. The median first day of coma occurred on the sixth day of I. S. T. After the production of coma, the dose is reduced rapidly until no stupor or coma appears. This occurred in our series (on the average) on the 20th day of insulin shock therapy, with a range of 11 to 34 days (3d to 7th week) of insulin therapy. The dose is then maintained at the level which produces coma.

The daily schedule was as follows:

6:45 a. m. : Basal eosinophile count (7:00 a. m. count)

7:00 a. m. : Regular insulin intramuscularly and atropine, grain 1/150 (0.40 mg.), subcutaneously

9:00 a. m. : Stupor or coma usually occurring at this time

10:20 a. m. : Administration of Karo solution orally when possible

10:30 a. m. : Intravenous administration of 35 cc. of 25% dextrose if patient was too deep in coma to drink

11:00 a. m. : Shower and breakfast

1:00 p. m. : Eosinophile count

after the injection of insulin. Three to 5 ml. of venous blood was collected in a tube containing a dried balanced oxalate mixture. A 1:20 dilution of the blood was made in a calibrated leucocyte pipette, using the diluting fluid described by Pilot.[6] Counts were then made, using two double Levy counting chambers of 0.2 mm. cell depth, and an area of 16 sq. mm. each was counted. The average of the four chambers was multiplied by 6.25.

Plasma 17-hydroxycorticosteroids were determined by a modification of the method of Nelson and Samuels[7] in an additional three patients at 1 week before and on Monday of the 3d, 6th, and 11th weeks of shock therapy, and at the 2d and (in two subjects) at the 14th week following the last day of therapy. Blood samples were taken in citrated containers at 7:00, 10:00, and 11:30 a. m. Eosinophile counts were made at 7:00 a. m. and 1:00 p. m.

D. Statistical Analysis.—Statistical analyses were made by standard techniques (Fisher). Arithmetic means were compared by the *t* test, although the distribution of eosinophile cell counts in a group of subjects is neither normal nor symmetrical but is

TABLE 1.—*Status and Treatment of Improved and Unimproved Groups*

					Schizophrenia Classification *			Initial Eos. Count † per Cu. Mm.		Course I. S. T.		E. S. T.‡	
	M	F	Month Since Onset	Age	S. P.	S. C.	Other	Mean	S. E. Mean	10 Wk. No. Pt.	12 Wk. No. Pt.	No. Pt.	Av. Shocks per Pt.
Improved (23) §	20	3	60 (4-135)	31 (21-46)	19	2	2	240	± 32	11	12	17 (76%)	7
Unimproved (12)	10	2	55 (12-123)	28 (21-37)	6	2	4	206	± 27	9	3	8 (67%)	8

* S. P. = paranoid schizophrenia; S. C., catatonic schizophrenia; other, simple and hebephrenic forms.
† Eosinophile count per cubic millimeter of blood at 7:00 a. m. on day insulin shock therapy (I. S. T.) was initiated.
‡ E. S. T. means electroshock therapy was given as supplementary therapy to some patients during latter portion of a course of I. S. T.
§ See text for criteria. Four patients relapsed within two months of end of course of I. S. T.

Electroshock therapy combined with I. S. T. was given to some patients if, in the judgment of the psychiatrists in charge of therapy, the patient did not seem to be showing adequate improvement by the sixth to the seventh week. This treatment was usually given at 10:00 a. m., three times a week (Table 1). Insulin was not administered on Sundays in the 10-week course of therapy or on Saturday or Sunday in the 12-week course of therapy. It was also omitted on national holidays and on a few occasions because of clinical complications.

C. Laboratory Studies.—Eosinophile counts were done before and after the course of I. S. T. and on Monday and Friday throughout the course of insulin shock therapy, except that in 16 of the total of 354 weeks counts were made on appropriate substitute days because of holidays or other factors. The count taken between 6:45 and 7:00 a. m. was called the basal count, or 7:00 a. m. count. Blood specimens also were taken at 1:00 p. m., six hours

skewed to the right. It has been suggested that logarithmic analysis be used.[8] However, the normality of the random sampling distribution of means is not contingent on the normality, or even the symmetry, of the actual distribution of observations for samples of the sizes used, and since an arithmetic analysis is more easily understood and more widely used than a logarithmic analysis, arithmetic, rather than logarithmic, means were compared.

RESULTS

A. Preliminary Observations in Schizophrenics.—1. Relationship of Time Since Onset of Psychosis, Time Since Last Shock Treatment, and Age to Basal Eosinophile Count: The basal (7:00 a. m.) eosinophile counts were examined in a larger group than the experimental group discussed in this

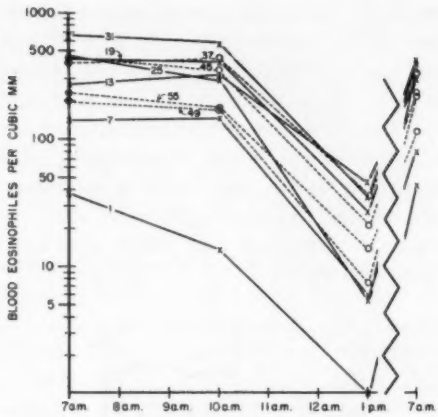


Fig. 1.—Blood eosinophile count at 7:00 a. m. on Monday and at intervals throughout the next 24 hours during the course of insulin shock therapy in a schizophrenic man.

This chart shows, on a semilogarithmic graph, the fall in eosinophiles found at the sixth hour (1:00 p. m.) after the injection of insulin, the insignificant fall three hours (10:00 a. m.) after the injection of insulin, and the rise to approximately the basal level or higher 24 hours after the injection of insulin. The slope of the lines between the 10:00 a. m. and 1:00 p. m. counts indicates that the percentage fall was approximately the same on the various Mondays. Also to be noted is the rise in the basal (7:00 a. m.) count, reaching a peak on the 31st day of insulin shock therapy, and the fall thereafter. The day of insulin shock therapy is indicated by the number on the line. The latter half of the course of insulin shock therapy is indicated by the dotted lines.

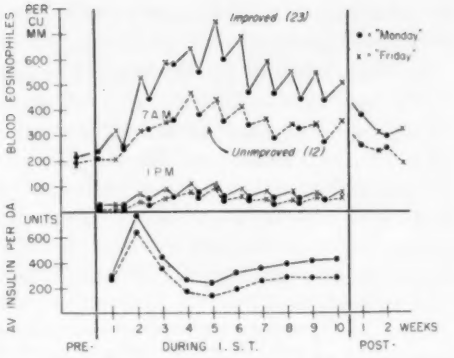


Fig. 2.—Course of the eosinophiles and insulin shock therapy (I. S. T.).

The chart shows the mean basal (7:00 a. m.) and six hours' postinsulin (1:00 p.m.) eosinophile counts on Monday and Friday throughout the course of insulin shock therapy, and the mean basal count two weeks thereafter for the improved (solid line) and the unimproved group (dashed line) of schizophrenic subjects. The mean basal count on Friday was consistently greater than the mean basal count on Monday throughout the course of I. S. T., but was not so before or after the course of I. S. T. The means of the 1:00 p. m. counts, post-therapy (not charted), were slightly lower than the respective means of the 7:00 a. m. counts for both the improved and the unimproved group. Counts before instituting therapy showed no significant difference of the 7:00 a. m. counts on Monday and Friday morning, and the 1:00 p. m. counts (not charted) were, in general, slightly lower than the 7:00 a. m. counts.

The lower section of the charts shows the mean insulin dose per day each week throughout the 10-week course of insulin shock therapy. Since only 12 of the 23 improved patients and 3 of the 12 unimproved patients had 12 weeks of I. S. T., the last 2 weeks of therapy in these patients are not charted. Figure 4 shows more clearly the relationship of the mean insulin dose per day each week to the mean of the basal eosinophile counts on Friday and Monday of each week.

paper. The counts were then analyzed in relationship to the time since the onset of psychosis and the time since the last course of insulin or electroshock therapy. The "onset" was considered to have occurred at that time when schizophrenic symptoms became severe enough to require medical attention.

The relationship of the mean basal eosinophile count to duration of psychosis and interval since last shock treatment are shown in Table 2.

These results indicate a significant increase in basal eosinophile count associated with schizophrenia of greater than 24 months' duration but do not necessarily mean that it is due to the "schizophrenic process." Examination of the basal eosinophile count in relation to age showed that there was no correlation. Table 1 shows that in this small series of 35 subjects the patients who improved had no significant difference in dura-

TABLE 2.—*Mean Basal Eosinophile Count/Cu. Mm. in 131 Schizophrenic Adults**

(Figures in parentheses indicate number of patients)

Time Interval	Less Than 24 Mo.	More Than 24 Mo.	Significance of Difference
Onset to observation	173 (22)	300 (109)	$P < 0.002$
Last shock treatment to observation	242 (44)	300 (87)	$P < 0.08$

* 126 men; 5 women.

tion of psychosis, age, or pretreatment basal eosinophile count.

2. Acute Effect of Insulin Shock Therapy on Eosinophile Count: Figure 1 shows a preliminary experiment in which the eosinophile count was made each Monday throughout the course of insulin shock therapy at 7:00 a. m., 10:00 a. m., and 1:00 p. m., and at 7:00 a. m. the next morning. Results are plotted on a semilogarithmic scale. These are found. The chart also indicates a feature more clearly shown in Figure 2, i. e., that basal eosinophile count gradually rose during the first portion of the course of I. S. T. and tended to fall during the latter portion. After this, and several similar experiments, of a preliminary nature, the 10:00 a. m. counts were omitted. These results, in general, are similar to those noted by Mann and Lehmann [9] and others.

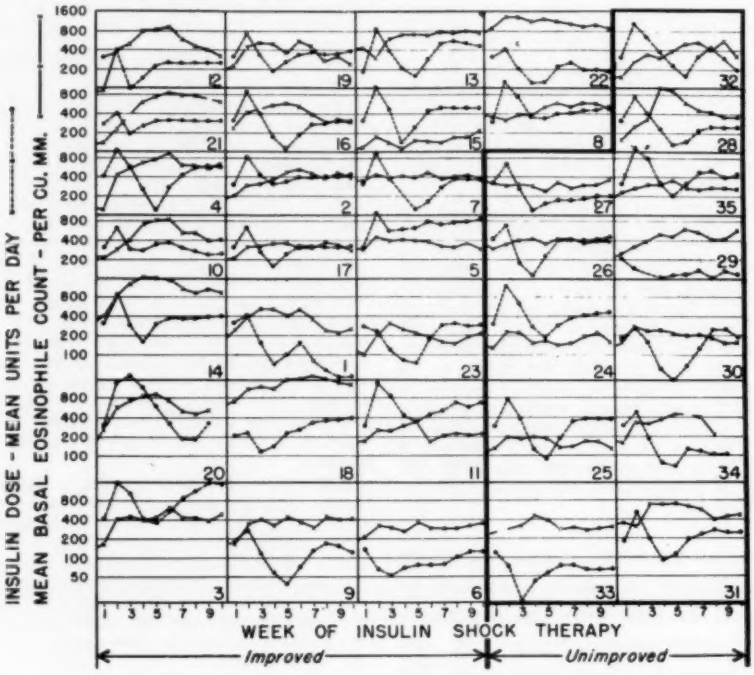


Fig. 3.—Individual observations: relationship of the basal eosinophile count and the average insulin dose each week throughout the course of insulin shock therapy.

This chart illustrates, on a semilogarithmic graph, the marked variability of basal eosinophile response and insulin dosage required. The sum of the basal eosinophile counts on Monday and Friday of each week was divided by two and plotted against the total insulin dose administered during the week, divided by the number of days on which it was administered.

indicate that there is very little fall, if any, by 10:00 a. m., three hours after the injection of insulin, and that the rate of fall between 10:00 a. m. and 1:00 p. m. is rapid and more or less the same throughout the course of insulin shock therapy, as indicated by the similarity of the slopes of the lines. In addition, there is a rise in the eosinophile count, so that by 7:00 a. m. the next morning the previous levels or somewhat higher levels

B. Course of Blood Eosinophiles During Insulin Shock Therapy.—Figure 2 shows the course of the mean 7:00 a. m. (basal) eosinophile count on Monday and Friday before, during, and for two weeks after termination of insulin shock therapy. Many individual curves showed a similar pattern, but variations were frequent and marked (Fig. 3). Rud [3] and others have described a somewhat similar pattern of re-

TABLE 3.—*Mean Eosinophile Count per Cubic Millimeter for Entire Course of Insulin Shock Therapy*

	Improved	Unimproved	Difference	S. E. Diff.
Monday counts.....	485	326	159	± 79
Friday counts.....	570	366	204	± 107
Monday and Friday minus initial.....	280	140	149	± 71

sponse. The improved patients had a significantly higher basal eosinophile count (at $P < 0.05$ level) on Monday in the 4th, 6th, 8th, and 10th weeks of therapy. In addition, as indicated in Table 3, the mean basal eosinophile count of the improved group was higher than that of the unimproved group (P approximately 0.05) on both Mondays and Fridays. The difference between the mean of all basal counts and the initial Monday count was also significantly greater in the improved group. However, there was no relationship between the degree of change in the basal eosinophile count and the level of improvement attained.

C. Relationship of Plasma Level of 17-Hydroxycorticosteroids and Basal Eosinophile Count.—Figure 4 shows the blood plasma levels of 17-hydroxycorticosteroids taken at 7 : 00 a. m. before, during, and after the course of insulin shock therapy. These values are plotted in relation to the eosinophile count taken at the same time. It will be noted that in two of the patients the plasma levels of 17-hydroxycorticosteroids decreased as the eosinophile count increased. However, in Patient Re. this relationship was not present.

This finding, in conjunction with the known effect of cortisone and hydrocortisone therapy on the basal eosinophile count, the inverse relationship of urinary corticoid excretion and eosinophile count following operative trauma,* and the changes noted in these measures in patients with Cushing's syndrome following successful therapeutic intervention, suggests that changes in the basal eosinophile level, at least in some patients, may reflect, to some extent, the changes in concentration of 17-hydroxycorticosteroids.

* References 1 and 10.

D. The Relationship of Basal Count on Monday Morning Compared with That on Friday Morning.—The mean basal Friday count was higher than the mean basal Monday count throughout the course of I. S. T. (Fig. 2). In the improved group, this relationship was present in 178 of the total of 245 weeks in which counts were made, and in the unimproved group, in 77 of 109 weeks of observation. This is approximately the same percentage for the two groups. The greater incidence of the higher Friday counts is significant at the $P < 0.001$ level. Variation in the Monday and Friday counts is suggestive of some decrease in adrenocortical activity during the period of each week when I. S. T. was administered (i. e., Monday through Friday or Saturday). Such variation did not occur before or after the course of I. S. T., nor is it found in normal men.[8]

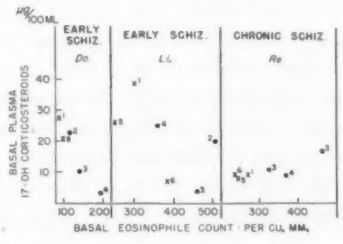
E. Acute Fall of Eosinophiles in Experimental Group.—The means of counts six hours after insulin injection (1 : 00 p. m.) for the improved and for the unimproved group are plotted in Figure 2. Counts at this time show the mean 1 : 00 p. m. Friday counts to be greater than the mean 1 : 00 p. m. Monday counts. However, the differences in these values are not as great as the differences in the basal counts. The group mean percent

Fig. 4.—Relationship of the basal eosinophile count and the basal plasma 17-hydroxycorticosteroid concentration.

Crosses indicate observations prior to or after termination of insulin shock therapy (I. S. T.); solid circles, observations during the course of I. S. T.

The numbers indicate the time at which the observations were made. Thus, *1* means 1 week before I. S. T.; *2*, 3d week of I. S. T.; *3*, 6th week of I. S. T.; *4*, 11th week of I. S. T.; *5*, 2d week after I. S. T., and *6*, 14th week after termination of I. S. T. Observations were made on Mondays at 7 : 00 a. m.

Note the relatively high initial 17-hydroxycorticosteroid values for Patients D. O. and L. I.



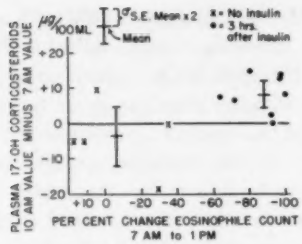


Fig. 5.—Relationship of the change in plasma 17-hydroxycorticosteroid concentration to the percent fall in eosinophile counts.

The intraindividual differences in concentrations of 17-hydroxycorticosteroids at 10:00 a.m. and those at 7:00 a.m. are plotted in relation to the percent change in the eosinophile counts (from the 7:00 a.m. to the 1:00 p.m.). The lines showing the mean change and 2 × S. E. of the mean change in the 17-hydroxycorticosteroid values are placed so as to indicate the mean percent change in eosinophile count.

In addition to the above, three observations were made prior to insulin shock therapy but are not included because eosinophile counts were not made at 1:00 p.m. These values showed changes (7:00 a.m. to 10:00 a.m.) of —13, —13, and +6 γ/100 ml. of plasma. A single observation (not plotted) on another subject, during the course of I. S. T., showed a rise of 10 γ/per 100 ml. of plasma (7:00 a.m. to 10:00 a.m.) and a fall of 90% in the eosinophile count.

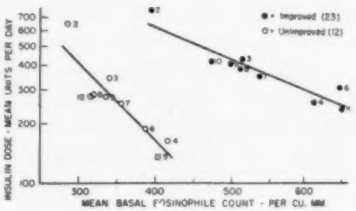
falls on Mondays were 88 and 89 for the improved and unimproved groups, respectively, while the mean Friday decreases were 84 and 85%. The mean percent fall of eosinophiles on Monday was greater than the mean percent fall on Friday for 19 of the 23 patients in the improved group and for 9 of the 12 patients in the unimproved group, making a total of 28 out of 35 for the combined groups. Analysis by the χ^2 technique indicates that this distribution is highly significant. It is obvious that the absolute fall is greater on Friday than on Monday, even though the percent fall is less, owing to the higher basal counts. The mean percent fall during the first few weeks of therapy was not significantly different from that in the last few weeks of therapy.

F. Relationship of Acute Change in 17-Hydroxycorticosteroids in Plasma to Acute Fall of Eosinophile Level.—In three patients the plasma 17-hydroxycorticosteroid values were measured on Mondays prior to I. S. T. and at the beginning of the 3d, 6th, and 11th weeks of insulin shock therapy and the 7th and 14th weeks after termination of I. S. T. Values were determined in specimens obtained at 7:00, 10:00, and 11:30 a. m. Figure 5 shows the increase or decrease of plasma 17-hydroxycorticosteroid values three hours after the 7:00 a. m. specimen. The mean rise in the plasma 17-hydroxycorticosteroid level from 7:00 a. m. to 10:00 a. m. during insulin shock therapy was 8.3 γ per 100 ml. of plasma (S. E. of mean ± 1.9). The mean fall of plasma 17-hydroxycorticosteroids from 7:00 a. m. to 10:00 a. m. prior to and after discontinuation of therapy was 3.7 γ per 100 ml. of plasma (S. E. of mean ± 4.24). These values are significantly different at approximately the $P = 0.03$ level. The mean fall of eosinophiles (7:00 a. m. to 1:00 p. m.) during insulin shock therapy was 88%. The mean fall prior to and after discontinuation of insulin shock therapy was 6%.

The mean increase in the 11:30 a. m. specimen (from the 7:00 a. m. specimen) was 5.7 γ during I. S. T., and the fall at 11:30 a. m. prior to and after I. S. T. was 2.2 γ (values not shown in Fig. 5). The P value for the difference of the means is approximately 0.1. A fall in plasma 17-hydroxycorticosteroid concentration during the morning has also been noted in normal persons.[11]

Fig. 6.—Relation of the mean daily insulin dose each week to the mean basal eosinophile count each week throughout the course of insulin shock therapy.

The data, when plotted on semilogarithmic graph, show a linear negative correlation. The position and slopes of the regression lines are significantly different. The possible significance of these relationships is considered in the discussion. The numbers by the symbols indicate the week of I. S. T. The first week is omitted, since the insulin dosage is primarily a routine matter until coma is produced. After induction of the first coma, the dose is manipulated (see "Methods") so as to produce coma with the minimum dose of insulin.



G. Relationship of Eosinophile Count to Insulin Dose Given to Produce Coma.—As indicated in "Methods," the mean daily dose of insulin for each week throughout the course of insulin shock therapy, after the first week, may be used as an index of the patient's "sensitivity" to insulin, since all doses after induction of the first coma (which usually occurs in the second week) are regulated according to the depth of coma produced by the previous dose. Figure 2 shows that there was a marked decrease in the mean daily dose of insulin required to produce coma, the lowest mean daily dose for both groups occurring in the fifth week of therapy. Figure 3 shows the variability of individu.l response. Following this, there was a slight increase in dose (decrease in "sensitivity"). Although such changes in sensitivity may be due to changes in the nervous system or elsewhere, it would seem at least equally probable that changes in concentration of "anti-insulin" factors may be responsible.

Figure 6 illustrates the inverse relationship of the mean daily dose of insulin each week and the mean of the basal counts on Monday and Friday of each week for the improved and unimproved groups during the 2d to the 10th week of therapy, inclusive. Inspection of Figure 3 demonstrates the individual variability in this relationship. The first week is not included in Figure 6, since coma is usually not produced until sometime during the second week of therapy, and the first week's dose is essentially a matter of routine technique.

COMMENT

Value and Limitations of the Eosinophile Count as Index of Adrenocortical Activity.—It is now well known that other factors than hydrocortisone, cortisone, epinephrine (even in the absence of adrenal cortex), and allergy influence the blood eosinophile count.† However, hydrocortisone, cortisone, and epinephrine appear to be the agents most likely to be associated with an acute fall in the eosinophile count.† Thus, the complete mechanism involved in the acute fall of eosinophiles following the administration of large doses of insulin is not known. However, the statistically significant rise in plasma 17-hydroxycorticosteroids occurring in the 10:00 a. m. specimen, three hours after insulin was given (compared with the slight fall during this three-hour period prior to and after the course of I. S. T.) is associated with a highly significant difference in the fall of eosinophiles exhibited by the two groups three hours later. This suggests that the fall in eosinophiles is, at least in part, due to the rise of plasma 17-hydroxycorticosteroids, since it has been demonstrated that cortisone or hydrocortisone and corticotropin injections will cause such a fall, and presumably the Porter-Silber reaction in plasma, as described by Nelson and Samuels,[7] is primarily due to hydrocortisone. However, the mean fall in eosinophiles approximately three hours after the measured change in the plasma 17-hydroxycorticosteroid values was 88% in our three patients, while Bliss, Nelson, and Samuels [11] found a somewhat smaller decrease after essentially comparable changes in plasma 17-hydroxycorticosteroids following intravenous corticotropin.

Thus, calculations from the data of Bliss and associates [11] demonstrate that one hour following the intravenous administration of 1 I. U. of corticotropin in 15 to 30 seconds there is a mean rise in 17-hydroxycorticosteroids of 9.5 γ per 100 ml. of plasma (three hours before the final eosinophile count), and one hour later a mean value only 3.3 γ above the initial values. These increases are roughly comparable to the increase of 8.3 γ in our 10:00 a. m. values (three hours before the final eosinophile count) and that of 5.7 γ in the 11:30 a. m. specimen. The percent fall in the eosinophiles, found by Bliss and associates,[11] four hours after the intravenous injection of 1 I. U. of corticotropin was 67%, a value having statistically significant difference from that of 37% found after placebo injections ($P < 0.02$). This suggests the possibility that the 88% fall in eosinophiles found in our patients after insulin may not be due entirely to changes in levels of 17-hydroxycorticosteroids. Epinephrine is

† References 1 and 2.

known to reduce the level of eosinophiles in adrenalectomized persons.[1] This, as well as other, factors must therefore be considered.

The quantitative importance of various factors affecting the basal eosinophile count is not clear. However, the fact that the resting 7:00 a. m. value of eosinophiles seemed to be crudely correlated with the absolute level of plasma 17-hydroxycorticosteroids (Fig. 4) in two of the three patients in whom these observations were made lends some support to the possibility that changes in the basal eosinophile count may, in part, reflect changes in blood plasma levels of 17-hydroxycorticosteroids before, during, and after a course of I. S. T. However, analysis of the data of Bliss and associates [11] in subjects with multiple observations fails to show a consistent intraindividual relationship in the basal (8:00 a. m., fasting) eosinophile count and the basal concentration of 17-hydroxycorticosteroids, nor do their data show the range of variation in basal values for 17-hydroxycorticosteroids found in our subjects D. O. and L. I. This suggests that this relationship may be noted only in situations involving fairly marked changes in adrenocortical secretion, such as that following major operations [10] or other severe stress,‡ and in the marked variations in the eosinophile count and plasma 17-hydroxycorticosteroid level noted if these observations are made at 3-hour intervals throughout a 24-hour period.[13]

The data of Bliss and associates [11] demonstrate that, although there is a significantly greater percent decrease in the eosinophiles following I. V. administration of corticotropin than that following placebo injections, the quantitative relationship between the percent decrease and the rise in 17-hydroxycorticosteroids is poor. It cannot thus be used as a quantitative index of changes in plasma concentration of adrenocortical hormones. The evidence presented above thus indicates that the eosinophile count must be considered only as a crude qualitative index that, on a group statistical basis, affords evidence of changes (in the opposite direction but of unknown amounts) in the concentration of plasma 17-hydroxycorticosteroids.

Speculative Assumptions Used in Analysis of Data.—Therefore, with these reservations in mind, we have analyzed the results from the speculative point of view (1) that the acute fall of eosinophiles is a crude qualitative index of the release by the adrenal cortex of hydrocortisone (and cortisone ?) in response to acute stress; (2) that the mean basal count (7:00 a. m.) is a crude qualitative index of the basal secretion of these substances into the blood stream, and (3) that the insulin dose necessary to produce coma is inversely proportional to the activity of "anti-insulin factors." (Growth hormone, in particular, should be considered, since limited evidence suggests that this may be more diabetogenic than adrenocorticotropic hormone.)

On the basis of these speculative assumptions, the data may be interpreted as indicating (1) that shock therapy during a given week decreased the basal secretion of hydrocortisone (and cortisone?), as indicated by the increase of the basal count on Friday (Fig. 2) but that this decrease in basal secretion is, in part, compensated for by the weekend rest (Fig. 2), and that the compensation is not complete, as indicated by the gradual rise in basal eosinophile level (Fig. 2); (2) that the ability to cause rapid release of hydrocortisone (and cortisone ?) into the blood stream (in sufficient quantity to produce the approximately maximum depression of the eosinophiles for the time period measured [1]) is not diminished by a course of insulin shock therapy, thus indicating that the productive capacity of the adrenal has not been completely inhibited; (3) that a change in rate of secretion (due to the effects of repeated "stress") of both adrenocorticotropic hormone and of growth hormone may be the mechanism, in part, responsible for the inverse correlation of the mean basal eosinophile count each week and the mean daily dose of insulin given each week to produce coma (Fig. 6); (4) that a relationship may

‡ References 1 and 12.

exist between the factors responsible for clinical improvement and the physiological mechanisms responsible for changes in the basal eosinophile count, since "significant" differences ($P = 0.05$) between the improved and the unimproved group have been demonstrated (Figs. 2 and 6 and Table 3).

GENERAL COMMENT

The above assumptions and extrapolations from the data are highly theoretical, and further study is needed to determine whether they are valid. However, they appear to us to be the most probable assumptions and interpretations in the light of present knowledge. The limitations of the eosinophile count as an index of adrenocortical activity have been discussed above. It is also recognized that "insulin sensitivity," as judged by production of coma, may not necessarily be directly related to insulin sensitivity, as judged by the changes in blood glucose following the injection of insulin.

The relationship of changes in the eosinophile response and changes in clinical aspects of psychoses has been discussed by Rud [3]; by Altschule,[4] Mann,[9] Freeman,[14] and their associates, and by others. Inspection of Figure 3 reveals that 2 of the 12 patients who failed to improve had a 200% increase or more in their basal eosinophile counts (mean of Monday and Friday counts) and that several of those who showed immediate improvement had essentially "flat" curves. It appears, from a review of the literature and the data presented herein, that the rise in eosinophile level during shock therapy has distinctly limited value as a prognostic index.

SUMMARY

Blood eosinophile counts were made at 7:00 a. m., before insulin injection, and at 1:00 p. m., six hours thereafter, on Monday and Friday of each week throughout the course of deep insulin therapy in a group of 35 schizophrenic patients.

1. Both the improved and the unimproved group showed a gradual rise in the mean Monday basal (7:00 a. m.) eosinophile count and the mean Friday basal eosinophile count in the early portion of insulin shock therapy, falling slowly about halfway to the initial count during the latter weeks of I. S. T. Individual variations from this pattern were frequent and marked.

2. The increase of the mean basal eosinophile count in the improved group was greater than that in the unimproved group ($P = 0.05$).

3. The basal Friday eosinophile counts for each group were higher than the basal Monday eosinophile counts in a highly significant proportion of the weeks during which counts were made.

4. There was a highly significant negative correlation between the mean basal eosinophile count and the mean daily insulin dose for each week. The slopes and the positions of the regression lines of the two groups were significantly different.

5. The basal plasma 17-hydroxycorticosteroid concentrations were apparently inversely correlated with the basal eosinophile levels in two of three schizophrenic men examined before, during, and after I. S. T.

6. A significant increase in the concentration of 17-hydroxycorticosteroids was found during I. S. T. three hours after insulin administration. This was associated with an average fall of 88% in blood eosinophile levels six hours after insulin administration. In the absence of administration of insulin, there was a slight fall in concentration of plasma 17-hydroxycorticosteroids and blood eosinophiles.

In general, it is believed that the data afford some support for the concept that with repeated severe stress there is a somewhat decreased basal secretion of adrenal cortex, possibly due to partial inhibition of the hypothalamic-anterior pituitary-adrenal cortex axis. The inverse correlation of the basal level of the blood eosinophile count and the marked changes in the amount of insulin necessary to produce coma suggest the possibility that the changes in insulin resistance may be due to concomitant changes in the basal secretion of the anterior pituitary (growth hormone and other anti-insulin

factors). It is suggested that the relationship of growth hormone and adrenocorticotropic hormone production to improvement of schizophrenia is a subject worthy of further investigation.

Hyman Menduke, Ph.D., Assistant Professor of Biostatistics, Jefferson Medical College, assisted in the statistical analyses; and Miss Doris M. Joslin, Medical Librarian at the Veterans Administration Hospital, and Miss Mary A. Garton, at the Hospital of the University of Pennsylvania, aided in the preparation of the manuscript. Mr. Kenneth Wolfe, Charge Nurse, Insulin Shock Clinic, Veterans Administration Hospital, Coatesville, Pa., gave invaluable assistance.

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TACTILE ADAPTATION DISTURBANCES IN LESIONS OF THE NERVOUS SYSTEM

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Sensations in nearly all modalities show the phenomenon of negative adaptation. That is, under continual and unchanging application of a given stimulus the characteristic sensation evoked disappears after a given interval. This interval is known as the sensory adaptation time.[1]

THE IMPORTANCE of the phenomenon of adaptation becomes evident when one considers that a large proportion of the stimuli that impinge on the individual during the course of his existence are not punctate in time, but may extend over considerable periods without changing in intensity. This may be readily demonstrated in the tactile modalities, but is also apparent in olfaction and vision. Sensory adaptation is probably also involved in the mechanism which enables us to know at all times the position of our limbs in space, and therefore to initiate discrete movements and to perform "temporally integrated actions," [2] such as writing and walking.

Most investigations of tactile adaptation have been performed by experimental psychologists and neurophysiologists, who have conceived of the phenomenon as a function of the end-organ and peripheral nerves. A great deal of detailed work has been done, introspectively and electrophysiologically, to elucidate the role of the peripheral structures. This emphasis leads to expressions such as the one appearing in a recent handbook: "Barring central processes [!] . . . [adaptation] . . . may be due to a change in the receptors, or to a change in the effective stimulus, or to some combination of the two." [3]

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Experimental studies on the adaptation of superficial pain were first reported in the United States by Murray,[4] whose findings were published in 1908. These studies were extended and confirmed by Straus and Uhlmann [5] and by Burns and Dallenbach.[6] Adaptation to superficial pain was shown to exist in the normal subject. There was, however, considerable variability in the performance of different subjects in terms of the time required for adaptation to stimuli of different weights. The work of these investigators was generally based on the assumption that adaptation is a function of the receptors and/or the nerve fibers. Recordings of the action potentials in afferent nerve fibers seem to indicate the operation of such a peripheral mechanism.* Nafe and Wagoner, however,† in a study of adaptation to pressure, go so far as to take the mechanism entirely out of the nervous system. They present evidence to show that "adaptation is due to loss of effectiveness of the stimulus rather than to any loss on the part of the end-organ."

Although peripheral mechanisms can be shown to be involved in sensory adaptation, they are certainly not the exclusive mechanism, and indeed may not be the determining one. It has been shown, for example, that disturbances in adaptation for somatosensory and visual functions occur in persons with lesions of the central nervous system. ‡ While this type of evidence cannot lead to positive conclusions about the normal mechanism of adaptation, negative conclusions can be drawn from the existence of abnormalities in adaptation when the peripheral structures are intact and the central nervous system has been injured.

Within recent years, evidence of this type has been presented by Bender,[1] Nathan,[16]

* References 7, 8, and 9.

† References 10 and 11.

‡ References 12 through 15.

and Ross and Fountain.[17] Bender [1] presented a series of patients who had suffered brain injury and who showed serious disturbances in somatosensory adaptation and after-sensation. Most of his subjects were battle casualties; they were examined within a few months of the time of injury and in general showed gross disturbances in several modalities of sensation.

The purpose of the present study was to extend the investigation of disturbances in sensory adaptation in persons with lesions of the central nervous system. In an attempt to find correlations between the degree of dysfunction and the locus and severity of the lesion, several groups of patients were examined. Comparative studies were also done on normal controls and on subjects with peripheral nerve lesions.

MATERIAL AND METHOD

The studies fell into two major classifications. The first studies were performed with a group of brain-injured veterans of World War II who were volunteer experimental subjects for the psychophysiological laboratory of the Department of Neurology, New York University-Bellevue Medical Center. These men were all ambulatory, and most were gainfully employed. The second group of studies was performed with hospitalized patients at the Bellevue and Mount Sinai Hospitals who had lesions of the brain, brain stem, and spinal cord. The methods and results for the two groups will be discussed separately.

I. *Experimental Subjects.* — This group of subjects consisted of 15 veterans of World War II. These men had suffered brain injury from five to eight years prior to the time of examination. Fourteen of them had penetrating cranial wounds with definite clinical evidence of brain injury. It must be emphasized that the degree of structural damage remains unknown! In some cases large amounts of cerebral tissue may have been destroyed, but in others a small missile fragment may have caused little more damage than that done by the passage of a ventriculography needle. The primary site of brain damage could be roughly localized on the basis of x-ray evidence of bone destruction and retained foreign bodies, the notes of the attending neurosurgeons, and, in some cases, the presence of gross neurologic signs. Thirteen of the subjects had definite evidence of parietal lobe involvement. In only one case, however, was the damage probably limited to the parietal lobe. The other subjects had, in varying degree, suffered additional damage to the frontal, temporal, or occipital lobe. The somatosensory functions of the subjects were evaluated in a series of tests. Both hands were tested for two-point discrimination, graphesthesia, stereognosis, touch, and pinprick sensibility. The subjects were also given the face-hand test by the method of double simultaneous stimulation.[18]

The apparatus for testing adaptation consisted of an upright bar with two arms, in the shape of a cross (a laboratory ring stand and two test tube clamps). Two plastic knitting needles were placed so that they could be freely raised and lowered, one passing through the opening at the end of each of the arms of the cross. An ordinary straight pin was fixed to the lower end of each of the knitting needles, which were weighted so that each weighed 8 gm.

During the adaptation test, the subject sat, blindfolded, at a table, with his forearms resting on the table, the hands turned palms down, one on each side of the base of the apparatus. The hands were placed so that the first interosseous space was directly under the end of the cross arm. Each hand was tested separately for adaptation in the following manner: The point of the pin was gently placed on the skin over the first interosseous space in such a manner that the knitting needle to which it was fixed was perpendicular, thus allowing the full weight of 8 gm. to be borne by the point. The pin was allowed to remain for 120 seconds, at the end of which time it was gently lifted. The subject had been instructed to report what he felt; his statements were recorded by the observer both during the period of stimulation and afterward as long as the

subject reported any sensation which was related to the stimulus.

After the hands had been tested separately, they were tested simultaneously. The procedure was identical with that described above, except that the pins were placed, and subsequently lifted from the two hands, simultaneously.

The "adaptation time" was recorded as the point at which the subject reported that he no longer was aware of the presence of the stimulus. In most cases, as previously reported,[6] the sensation of "sharpness" passed through diminishing grades of "touch" or "tickle" before complete adaptation took place.

TABLE 1 (Case 12).—*Adaptation to Pinprick: Severe Left Frontoparietal Lesion*

Time, Sec.	Left	Time	Right
	Single Stimulation		
0	"Pin"	0	"Pin"
20	"Same"	20	"Still feel it"
60	"Lighter"	60	"Less strong"
90	"Still there"	90	"Hurts more"
115	"Still there"	115	"Hurts more"
120	Pin lifted	120	Pin lifted
125	"It's off"	125	"It's off"
	Double Simultaneous Stimulation		
0	"Pin"	0	"Pin"
30	"Hurts"	30	"It's gone"
60	"Hurts"		
105	"Hurts"		
120	Pin lifted	120	Pin lifted
125	"It's off"	125	No sensation reported

Several normal subjects were tested according to the procedure described above. None of them showed complete adaptation within the given time of stimulation (two minutes). Additional control was derived, in the patients, from comparing the results obtained on the "affected" hand with those obtained on the "unaffected" hand.

The Data: Tables 1, 2, and 3 present examples of the protocols obtained in the brain-injured group.

Table 1 shows the responses of one of the subjects (Case 12) who had normal adaptation times when the hands were tested singly but who showed a definite abnormality when the hands were tested simultaneously.

The responses of a subject (Case 6) who had reduction in adaptation time under both conditions of testing are shown in Table 2.

A summary of the results of all the sensory tests is given in Table 3. The test in which the greatest number of subjects showed abnormal results was the "double simultaneous adaptation test." In three of the subjects this was the only objective abnormality. In most of the cases in which this abnormal response occurred, however, it was associated with one or another of the

TABLE 2 (Case 6).—*Adaptation to Pinprick: Left Parieto-Occipital Lesion*

Time	Left	Time	Right
	Single Stimulation		
0	"Pinprick"	0	"Pinprick"
15	"Touch"	20	"Gone"
30	"Touch"	30	"Back again, stronger"
60	"Touch"	45	"Weaker"
75	"Stronger"	60	"Gone"
90	"Faint touch"	75	"Nothing"
105	"Faint touch"	90	"Nothing"
		115	"Maybe a faint touch"
120	Pin lifted "Nothing"	120	Pin lifted "Nothing"
	Double Simultaneous Stimulation		
0	"Pin"	0	"Pin"
20	"Some"	20	"Duller"
45	"Touch"	45	"Touch"
60	"Touch"	60	"Touch"
90	"Touch"	90	"Gone"
110	"Faint touch"	110	"Nothing"
120	Pin lifted "Nothing"	120	Pin lifted "Nothing"

sensory defects elicited. Only two subjects (Cases 8 and 13) showed a large number of sensory defects. Both these men had severe left cerebral damage, with right hemiparesis and dysphasia present at the time of examination. They alone complained of severe symptoms of sensory impairment. The other subjects either had no symptoms at all or had vague complaints, such as "My right hand is more sensitive to hot and cold," or "My left little finger gets numb sometimes," or "Sometimes I tend to stumble in a dark room." It is significant that the second commonest positive finding was abnormal response on the face-hand test. Five of the subjects showed persistent "extinction" of the stimulus applied to the "affected" hand

when either the ipsilateral or the contralateral side of the face was simultaneously touched. In general, the abnormalities found in the "primary modalities" of sensation, and even in graphesthesia and stereognosis, were minimal, and often barely detectable with the ordinary clinical methods used.

The after-sensations were recorded for all subjects. There was a great deal of variability, which seemed related to personality factors rather than to the nervous system lesions or specific sensory defects. It was often impossible to ascertain, without risking undesirable prompting, whether the subject's report of "It's off" or "It's gone" meant that at that point he knew that the pin had been lifted, or that he no longer felt anything at all connected with the previous stimulation. The only consistent correlation obtained was that in the instances in which there was reduction in adaptation time there was no after-sensation. (The subjects occasionally reported a momentary "touch" or "scratch" sensation at the instant of removal of the pin.) §

II. *Hospitalized Patients.* — The patients included in this group had lesions at different levels of the central nervous system and were disabled in varying degrees. As a result of these factors, the standardized method of testing for sensory adaptation which was used in the experimental subjects could not be used in all these patients. In some cases the stimulus consisted of a safety pin, held in the examiner's hand and applied to various parts of the patient's body. The resultant inconstancy of stimulation would probably have obscured minimal findings such as those seen in the "experimental" subjects, but was not effective in preventing the elicitation of abnormally short adaptation times in the more acutely or severely incapacitated clinical subjects.

TABLE 3.—*Summary of Sensory Tests for Fifteen Brain-Injured Veterans*

Case No.	Decreased Adaptation Time: Single Stim.	Decreased Adaptation Time: DSS *	2-Point Discrim.	Graph-esthesia	Stereognosis	Touch Localization	DSS Face-Hand Test	Positive; Passive Motion	Vibration; Touch; Pinprick	Subjective Complaints: Minor	Subjective Complaints: Major	Total Positive Signs per Case
1	—	+	+	—	—	—	+	+	—	+	—	5
2	+	+	—	—	—	—	—	—	—	—	—	2
3	+	+	—	—	—	—	—	—	—	—	—	2
4	—	+	—	—	—	—	+	—	—	+	—	3
5	—	+	—	—	—	—	—	—	—	+	—	2
6	+	+	—	—	—	—	—	—	—	—	—	2
7	—	+	+	—	—	—	+	—	—	—	—	3
8	—	+	+	+	+	+	+	+	+	+	+	10
9	—	+	—	+	—	—	—	—	—	+	—	3
10	+	+	—	—	—	—	—	+	—	—	—	3
11	—	+	—	—	—	—	—	—	—	+	—	2
12	—	+	—	—	—	—	—	—	—	—	—	1
13	—	+	+	—	+	+	+	+	+	+	+	9
14	—	—	—	—	—	—	+	—	—	—	—	1
15	+	—	—	—	—	—	—	—	—	—	—	1
Positive cases per sign	5	13	4	2	2	2	6	4	2	7	2	..

* Double simultaneous stimulation.

CASE 16.—L. W., cerebral lesion.‖

A 62-year-old business man was admitted to the Mount Sinai Hospital complaining of "numbness" of the right hand, speech difficulty, and loss of memory. Eight years prior to admission he experienced an episode of clumsiness and inability to identify objects with the right hand. The symptoms cleared in a few months but recurred at intervals during the ensuing years. Five months before admission the "numbness" of the right hand reappeared and became slowly severer. He was unable to identify coins, keys, etc., when reaching into his

§ Bender [1] reported on a case of prolongation of adaptation time, with exaggeration of after-sensation. These phenomena were not seen in the present series.

‖ Case reported by courtesy of Dr. M. B. Bender.

pocket. Three months before admission he noticed occasional "searching for words," difficulty in calculation, and memory loss. He was unable to write clearly and made many mistakes on attempting to use a typewriter. There were no visual or auditory complaints, or complaint of weakness.

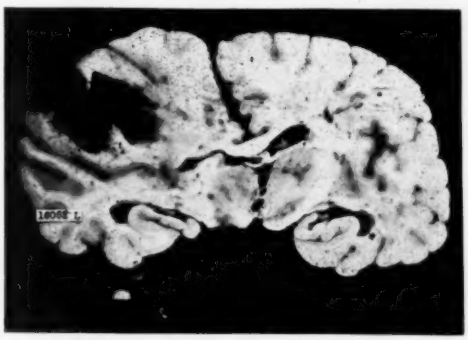
On neurological examination he showed a moderate degree of mixed aphasia, with predominantly expressive features. He was fully oriented, but showed definite defects in remote memory, marked difficulty in calculation, and a mild degree of finger agnosia. Motor signs limited to slight diminution in associated movements on the right side, and slight weakness in the right hand grip.

TABLE 4 (Case 16).—*Adaptation to Pinprick: Left Parietal Tumor*

Time	Left	Time	Right
	Single Stimulation		
0	Sharp	0	Sharp
15	Same	15	Less
30	Same	30	Maybe a touch
60	Less sharp	45	Nothing
75	Less sharp	60	Nothing
90	A little sharper	75	Nothing
115	Dull pressure	90	Nothing
		115	Nothing
120	Pin lifted "Nothing"	120	Pin lifted "Nothing"
	Double Simultaneous Stimulation		
0	Sharp	0	"A touch . . . something"
10	Sharp	10	Nothing
30	Sharp	30	Nothing
45	Sharp	45	Nothing
60	Less sharp	60	Nothing
75	Less sharp	75	Nothing
90	Sharp	90	Nothing
105	Duller	105	Nothing
120	Pin lifted "Off . . . nothing"	120	Pin lifted "Nothing"

Detailed sensory examination revealed the following changes: 1. Cotton-wool touch perception impaired over the right hand. 2. Pinprick perceived normally. 3. Vibration of 128 d. v. (C.) tuning fork perceived for 9 seconds over the right index finger, for 16 seconds over the left index finger, for 10 seconds over the right great toe, and for 19 seconds over the left great toe. 4. Rapid passive motion perceived in the right fingers and toes; slow passive motion not perceived. 5. Many errors in identification of position in the right fingers and toes. 6. Marked difficulty in identifying common objects held in the right hand. 7. Two-point threshold of 3 mm. on the left middle finger tip. Only one (the proximal) of two stimuli reported over the right hand, maximum distance between stimuli being 15 cm. 8. Errors on touch localization, with proximal displacement, over the right hand and lower forearm. Localization accurate over more proximal structures. 9. Persistent and severe form of extinction and displacement of tactile stimuli to the right hand on double simultaneous stimulation. 10. Difficulty in roughness discrimination with the right hand. 11. Perception of addition of 3 to 4 gm. weight in the left hand, and addition of 50 gm. weight to the right hand. On bilateral simultaneous stimulation, with 50 gm. weight in the left hand, he was unaware of 300 gm. in the right hand. Rapid adaptation to weight shown by lack of awareness of change in weight during the gradual addition of 300 gm., in 50-gm. increments, to 50 gm. already present in the right hand. 12. Marked disturbance in adaptation to pinprick (Table 4).

Four days after admission left carotid arteriography was performed, revealing the presence of a space-taking lesion in the left parietal lobe. During the next three days the patient became more aphasic and began to show more weakness of the right extremities. On the seventh hospital day he was operated on, and a large tumor was seen to



Left parietal tumor (Case 16). Hemorrhagic area following surgical extirpation of lesion.

be presenting on the surface of the left parietal lobe. A considerable amount of tumor tissue was aspirated. On the following day the patient died. At autopsy, section of the brain revealed a large hemorrhagic cavity, centered in the white matter of the left parietal lobe, extending from the surface to the wall of the lateral ventricle and extending forward and backward, in a tapering fashion, into the posterior frontal and occipital lobes, respectively.

Microscopic Diagnosis: "Relatively anaplastic oligodendroglioma" (Figure).

The predominant disabilities in this patient with parietal lobe lesion appeared to be defects in complex tactile functions. Each of the tests which involved the spatial or temporal integration of tactile-kinesthetic data brought out the functional deficit.

CASE 17.—R. K., intramedullary lesion of the pons.

A 65-year-old diabetic, arteriosclerotic woman who had been under treatment at the Mount Sinai Hospital for recent myocardial infarction. Sudden onset, on June 14, 1954, of severe vertical headache and "noises in both ears, worse in the left than in the right." Face "pulled over" to right. Occasional diplopia on right lateral gaze. No localized weakness.

Neurological examination on June 21, 1954, revealed the following: (1) horizontal nystagmus on left lateral gaze, rotary nystagmus on right lateral gaze; (2) severe left facial paralysis, "peripheral" type; (3) questionable decrease in auditory acuity; (4) hypalgesia to pinprick over right side of face and entire body. Cotton wool applied to right cornea elicited minimal blink response, with comment, "I feel the touch, but it doesn't hurt." Slight diminution in perception of light touch on right side of body. Position, passive motion, and vibration well perceived. Stereognosis normal. No defect on tactile testing by the method of double simultaneous stimulation. Two-point threshold 5 mm. on right middle finger tip; 3 mm. on the left. Marked disturbance in adaptation to pinprick (Table 5).

TABLE 5 (Case 17).—*Adaptation to Pinprick: Pontine Lesion*

Time	Left	Time	Right
	Single Stimulation		
0	Sharp	0	Touch
15	Touch	10	Light touch
30	Touch	15	Nothing
45	Sharp again	30	Nothing
60	Touch	45	Nothing
	Pin removed		Pin removed
	Nothing		Nothing
	Double Simultaneous Stimulation		
0	Sharp	0	Touch
15	Sharp	15	Nothing
30	Touch	30	Nothing
45	Touch	45	Nothing
60	Touch	60	Nothing
	Pin removed		Pin removed
	"Nothing"		"Nothing"

The prominent defects in this patient with a pontine lesion appeared to be those in the "primary" modalities of sensation (touch and pinprick), but she showed a marked reduction in adaptation time.

CASE 18.—J. G., spinal cord lesion.

The patient was a 63-year-old man who complained of progressive weakness and wasting of his right arm during the two years prior to his admission to Bellevue Hospital. On questioning, he stated that he had occasional "pins and needles" sensations in his hand, but he had no symptoms referable to sensory loss. On examination, the patient showed atrophy, weakness, and fasciculations of the right upper extremity, more marked proximally than distally. These signs were also present, to a minimal degree, in the left upper extremity. Deep tendon reflexes were increased on both sides, but were greater on the right. The right biceps jerk was absent. There was a Babinski sign on the right. Sensory examination revealed loss of pinprick sensation over both shoulders, in the distribution of cervical roots 2, 3, and 4. Temperature sensation was lost over the same area, but touch perception was normal. Two-point threshold in the finger tips was slightly raised, but graphesthesia, stereognosis, touch localization, face-hand test, sense of position and passive movement, and perception of vibration were normal. Lumbar puncture revealed a complete block on jugular compression. There were gross disturbances in adaptation to pinprick in the hands (Table 6), with even greater decrease in adaptation times over the shoulders, where the pinprick was perceived initially as "touch," with complete adaptation in less than 10 seconds.

TABLE 6 (Case 18).—*Adaptation to Pinprick: High Cervical Cord Lesion*

Time	Left	Time	Right
	Single Stimulation		
0	"Pin"	0	"Pencil point"
10	"May be gone"	15	"Something dull"
15	"Nothing there"	20	"Something dull"
		30	"Nothing at all"
60	"Nothing"	60	"Nothing"
120	Pin lifted; momentary "pin"	120	Pin lifted; momentary "touch"
	Double Simultaneous Stimulation		
0	"Pin"	0	"Dull point"
15	"Lighter"	15	"Lighter"
30	"It's gone"	30	"It's gone"
90	"Nothing"	90	"Nothing"
120	Pin lifted "Felt something" for an instant	120	Pin lifted "Felt something" for an instant

A patient on the Neurology Service of the Mount Sinai Hospital who presented similar evidence of intramedullary disease of the cervical segments of the spinal cord was tested for adaptation to pinprick. Again, the results were abnormal, the patient showing complete adaptation in 10 seconds in one hand and in 30 seconds in the other.

III. *Peripheral Nerve Lesions.*—Ten World War II veterans who had sustained peripheral nerve injury in the upper extremities were also tested for adaptation to pinprick. The extent of the original injury and the degree of functional recovery varied greatly among the subjects, but all 10

patients with peripheral nerve lesions showed some abnormalities in sensation when tested for touch and pinprick. Only three of them, however, had unequivocal abnormalities when tested for adaptation to pinprick. One of these subjects was a man whose left radial nerve had been severed and subsequently repaired, just above the elbow. At the time of the examination the only objective abnormality was an area of dysesthesia on the dorsal surface of the left hand. In this area pinprick stimulation caused a diffuse "itching" sensation, although the pinpoint could be readily distinguished from the sharpened point of a lead pencil. The adaptation results in this case are given in Table 7. It can be seen that the adaptation time in the affected hand is more "normal" under conditions of double simultaneous stimulation than on one single stimulation. This phenomenon was seen in only one of the brain-injured subjects (Case 15).

TABLE 7 (M. C.).—*Adaptation to Pinprick: Left Radial Nerve Injury*

Time	Left	Time	Right
	Single Stimulation		
0	"Prick"	0	"Point"
5	"Nothing"	30	"Same"
30	"Nothing"	45	"Slightly duller"
90	"Nothing"	60	"Slight prickling"
120	Pin lifted "Felt a little scrape"	90	"Dull, with surges of prickliness"
		110	"Fades and returns"
		120	Pin lifted "Felt a touch"
		135	"Very dull"
		150	"Very dull and light"
		165	"May be off"
		180	"Very light, like after-feeling"
		240	"Very faint"
		270	"Gone"
	Double Simultaneous Stimulation		
0	"Prickliness"	0	"Point"
10	"Nothing"	10	"Point"
30	"Itch" (mislocalized)	30	"Duller"
90	"Faint itch"	90	"Dull point"
115	"Very faint itch"	115	"Very light point"
120	Pin lifted "Felt relief of pressure"	120	Pin lifted "Felt relief of pressure"
150	"Nothing"	150	"Faint tingling"
180	"Nothing"	180	"Faint tingling"
205	"Nothing"	205	"Nothing"

COMMENT

The results of the present study serve to confirm the view that cutaneous adaptation is not a unique property of the end-organs and peripheral nerves. On the contrary, the degree of dysfunction seen after injury to the various levels of the nervous system seems to indicate the existence of a hierarchy, with defects in adaptation becoming increasingly apparent with greater involvement of the more centrally located integrative processes.[19] This point is specifically supported by our results in the peripheral nerve injury group. In spite of the existence of objective evidence of damage to the peripheral structures, this group showed the smallest incidence of disturbances in adaptation. By contrast, the severest and most disabling disturbances in tactile adaptation were seen in the patient with a parietal lobe tumor. It seemed that in this patient a defect could be demonstrated in every function which required the temporal and/or spatial integration of tactile-kinesthetic stimuli. These observations have been confirmed in several other patients with lesions of the parietal lobe. Since these studies were relatively incomplete, they were not included in this series.

Further evidence in support of the importance of central processes may be derived from the fact that more of the subjects showed disturbance in adaptation when tested by the method of double simultaneous stimulation than when tested one hand at a time. This finding is consistent with the significance of bilateral interaction in tactile perception, as shown in studies of both normal and brain-injured subjects by Bender,[18] Critchley,[20] Cohn,[21] and others. # It should be noted that in studies of extinction on double simultaneous stimulation there was also a hierarchy in which extinction was found most frequently and in most pronounced form in cases with lesions of the parietal lobe. The least pronounced deficit was found in cases with peripheral nerve lesions. Thus, defects in adaptation and

Reference 22 and 23.

extinction as a result of sensory interaction appeared to parallel each other in the hierarchy of defects in structure. Our clinical experience indicates that when markedly reduced adaptation time is found in association with extinction in a focalized area of the somatosensory field, there is a great probability that the parietal lobe opposite the side of the defect is involved.

It may be deduced from our data that the central nervous system does not serve merely to transmit and register impulse patterns arising in the periphery, but that central processes actively participate in determining the perception resulting from any given stimulus. Lashley [2] has recently described this interaction in these terms:

> The input is never into a quiescent or static system, but always into a system which is already actively excited and organized. In the intact organism, behavior is the result of interaction of this background of excitation with input from any designated stimulus.

The operation of this principle may be clearly demonstrated in visual, as well as tactile, perception. In the case of vision there is also a complex peripheral (retinal) mechanism which may be invoked to explain adaptation phenomena. The studies of Bay,[15] however, indicate that under conditions of brain injury a prominent central factor operates. He has shown that the normally present phenomenon of "local adaptation" (the "fading" of a stimulus object held motionless in the visual field) is markedly increased in subjects with lesions of the central visual pathways. Analogous findings have been presented by Krieger and Bender,[24] who found consistent abnormalities in dark adaptation in patients with occipital lobe lesions.

An experimental approach to this problem has been made by Adrian,[25] who presented evidence of a mode of interaction of peripheral and central structures. He recorded simultaneously from the olfactory nerve and the olfactory bulb of the rabbit.

> The olfactory bulb of the rabbit shows potential oscillations of two kinds: induced waves set up by strong olfactory stimuli and intrinsic waves due to the persistent activity of cells in the bulb. . . . As the anesthesia becomes lighter the olfactory signals regain control to some extent. They disorganise the rapid intrinsic rhythm of the bulb and suppress the persistent discharge of impulses in favour of the olfactory discharge at each inspiration. Ultimately, however, the intrinsic activity builds up again and the persistent discharge returns, swamping the transmission of the olfactory signals.
>
> As there is no sign of failure of the receptors under repeated stimulation at each breath, it is suggested that the weakening and ultimate failure of sensation in man (olfactory adaptation) is due to this reappearance of the intrinsic activity after its initial disorganisation.

In general, both experimental and clinical studies indicate that tactile adaptation is not a unique function of the peripheral structures, but is determined by a complex interaction of central and peripheral processes. Similarly, the apparent demonstration of adaptation phenomena specific for the modalities tested appears more likely to be due to the methods of testing than to the existence of modality-specific mechanisms within the nervous system. It is more probable that negative adaptation phenomena are expressions of some general principle of nervous system function.

SUMMARY AND CONCLUSIONS

A study of adaptation to pinprick was carried out on 18 subjects with lesions of the central nervous system and 10 with peripheral nerve injuries. A reduction in adaptation time was found in almost all the subjects with CNS lesions, particularly on testing by the method of double simultaneous stimulation. Those subjects with relatively large or progressive lesions involving the parietal lobe showed the greatest defects. Only three of the subjects with peripheral nerve lesions showed reduction in adaptation time.

These findings are discussed in relation to adaptation as conceived in terms of current theories of sensory function. Although studies of dysfunction following lesions cannot be directly invoked to explain normal physiology, the results obtained seem to indicate the operation of significant central factors.

A portion of this study was performed while I was serving as Post-Doctoral Fellow, U. S. Public Health Service. Dr. Morris B. Bender gave aid and guidance in the performance of this study and the preparation of the report.

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"PROTEIN PROFILE" IN MULTIPLE SCLEROSIS

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IN PREVIOUS studies* a characteristic pattern of protein changes was observed both in the blood serum and in the cerebrospinal fluid in about 80% of the patients with typical multiple sclerosis. The changes in these biological fluids examined simultaneously were termed the "protein profile." The variations in serum proteins, as determined electrophoretically,[1] consisted of significantly decreased albumin and A/G ratio values, markedly increased alpha-2 and beta globulin fractions, a slightly elevated (or normal) gamma globulin fraction, and a normal alpha-1 globulin fraction. Similarly, the cerebrospinal fluid proteins in the same patients showed markedly elevated total protein and gamma globulin values, as well as increased gamma globulin-total protein (G. G./T. P.) ratios.

The present study was undertaken to enlarge our case material for purposes of statistical analysis and to investigate changes of the "protein profile" in comparison with the clinical findings, over extended periods of time. Furthermore, the use of a simple graphic method, the "serogram," is employed for the evaluation of serum protein changes in multiple sclerosis, as previously described for other diseases.[3]

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From the Division of Laboratories and Department of Neurology, Jewish Chronic Disease Hospital.

* References 1 and 2.

MATERIAL AND PROCEDURES

1. *Selection of Patients.*—Forty-three patients were carefully selected for this study according to the diagnostic criteria characteristic for multiple sclerosis as previously defined.[1] Of these, 32 were patients from this institution (Jewish Chronic Disease Hospital), whose ages ranged from 28 to 72 years (average, 49 years) and whose disease process extended over a 6- to 35-year period (average, 22 years). The other 11 were patients from the Veterans Administration Hospital in Brooklyn, whose ages varied from 28 to 41 years (average, 32 years). The duration of the disease in this group ranged from 2 to 12 years (average, 8 years). In 28 of these 43 patients, on whom repeat determinations of the "protein profile" were carried out, a careful reevaluation of the clinical status was performed simultaneously with the biochemical studies. These repeat studies were carried out after an interval of 2 to 24 months had elapsed. In addition, a group of 12 healthy subjects served as controls for the electrophoretic serum protein data. Repeat studies were also carried out on this control group after a period of four to eight months.

2. *Biochemical Studies.*—(*a*) Serum Proteins: The methods used for the electrophoretic studies have been described previously.†

(*b*) Cerebrospinal Fluid Proteins: The procedure used for determination of the gamma globulin consisted of the protein flocculation-ninhydrin method[5] recently published from this laboratory. The total proteins were determined photometrically by a modification of the Weichselbaum method.[6]

RESULTS

1. *Serum.*—(*a*) Normal Subjects: The electrophoretic serum protein data obtained for our group of 12 normal subjects (22 determinations) as compared with the results of other investigators‡ who employed similar experimental conditions are shown in the accompanying Table. The mean values of some of the individual fractions show occasional disagreement among the various authors listed. However, the close correlation be-

† References 1 and 4.

‡ References 7 through 10.

Compilation of Electrophoretic Protein Data for Normal Human Serum as Determined in Barbiturate Buffer (pH 8.6 and 0.1 Ionic Strength)

No. of Sera	Total Protein, Gm./100 Ml.	Albumin, Gm./100 Ml.	Globulins, Gm./100 Ml.				A/G Ratio
			Alpha-1	Alpha-2	Beta	Gamma	
12 *.....	6.90 ± 0.48	4.00 ± 0.28	0.32 ± 0.04	0.63 ± 0.09	1.05 ± 0.16	0.89 ± 0.21	1.38 ± 0.15
43 †.....	7.29 ± 0.35	3.88 ± 0.23	0.58 ± 0.10	0.76 ± 0.10	1.01 ± 0.14	1.05 ± 0.22	1.15 ± 0.12
60 ‡.....	7.22 ± 0.48	4.10 ± 0.32	0.50 ± 0.09	0.60 ± 0.14	0.90 ± 0.28	1.00 ± 0.20	1.33 ± 0.18
13 §.....	7.23 ± 0.20	4.33 ± 0.21	0.25 ± 0.08	0.64 ± 0.10	0.93 ± 0.13	1.06 ± 0.18	1.49 ± 0.36
22 ‖.....	7.35 ± 0.25	4.23 ± 0.36	0.47 ± 0.07	0.65 ± 0.09	1.00 ± 0.13	1.00 ± 0.16	1.37 ± 0.20
(12 cases)							
149.....	7.26 ± 0.39	4.07 ± 0.29	0.48 ± 0.09	0.66 ± 0.11	0.96 ± 0.20	1.01 ± 0.20	1.30 ± 0.18
(140 cases)							

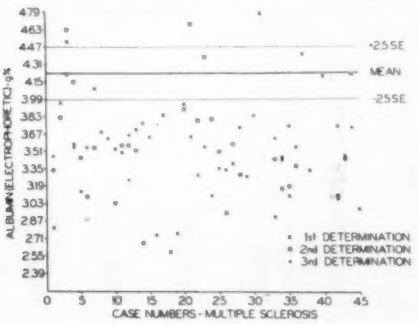
* Data from Benditt and Walker.[8]
† Data from Seibert, Seibert, Atno, and Campbell.[9]
‡ Data from Reiner, Fenichel, and Stern.[7]
§ Data from Cooper, Craig, and Beard.[10]
‖ Data from present investigation.

tween the mean values and standard deviations (S. D.) for the 140 normal subjects and for our small group of healthy persons provides sufficient justification for the use of our data as the base line for statistical evaluations of pathological conditions.

(*b*) Multiple Sclerosis Patients: The results obtained for the various protein fractions of sera from the 43 patients with multiple sclerosis, including repeat studies, are shown in the form of scattergrams in Figures 1 to 5. The conclusions derived from a statistical analysis for each protein fraction for these 43 multiple sclerosis cases, as compared with the normal series, are given in the legend under each graph. It can be seen that significant variations of the multiple sclerosis cases as a group, as compared with the normal series, are found in the following fractions: albumin, the alpha-2 and beta globulins, and the A/G ratio. Since the serum total protein values (micro-Kjeldahl) and the electrophoretic alpha-1 globulin fraction showed no significant deviations from the normal, no graphs for these components are included. Although the gamma globulin fraction in multiple sclerosis is of borderline significance statistically, a scattergram of the values is presented because of the markedly increased values obtained for this fraction in the cerebrospinal fluid.

Fig. 1.—Scattergram of electrophoretic serum albumin fraction in 43 cases of multiple sclerosis (79 determinations), including repeat studies on the same patients performed from 2 to 24 months later.

Statistical Data: Mean = 3.56 ± 0.46 S. D.; S. E. = ± 0.05; S. T. = 7.2; Est. Range of Pop. = 3.41 to 3.71 gm. per 100 ml. The normal mean and the estimated range for the normal population are indicated in the Figure.



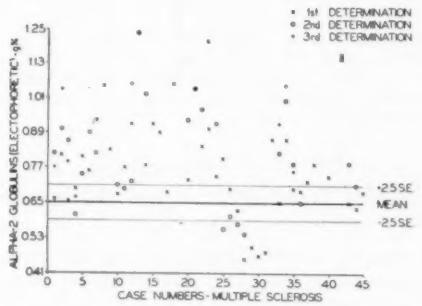


Fig. 2.—Scattergram of electrophoretic serum alpha-2 globulin fraction in 43 cases of multiple sclerosis (79 determinations), including repeat studies on the same patients performed from 2 to 24 months later.

Statistical Data: Mean = 0.81 ± 0.21 S. D.; S. E. = ± 0.02; S. T. = 5.2; Est. Range of Pop. = 0.74 to 0.88 gm. per 100 ml. The normal mean and the estimated range for the normal population are indicated in the Figure.

As can be noted in Figure 1, the serum albumin fraction is significantly decreased below the expected range of the normal popu-

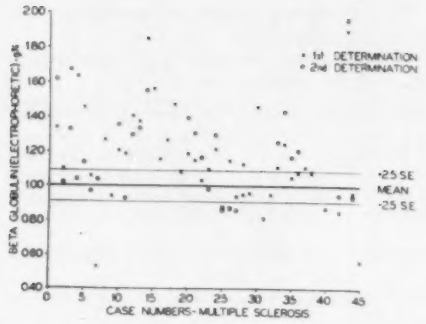


Fig. 3.—Scattergram of electrophoretic serum beta globulin fraction in 43 cases of multiple sclerosis (79 determinations), including repeat studies on the same patients performed from 2 to 24 months later.

Statistical Data: Mean = 1.20 ± 0.23; S. E. = 0.02; S. T. = 5.3; Est. Range of Pop. = 1.13 to 1.28 gm. per 100 ml. The normal mean and the estimated range for the normal population are indicated in the Figure.

lation in 85% of 79 determinations. For the individual cases, 86% of the 43 patients' values in the first series were significantly decreased, whereas 82% in the 28 repeat cases showed a similar result. The scattergram of the alpha-2 globulin fraction, illus-

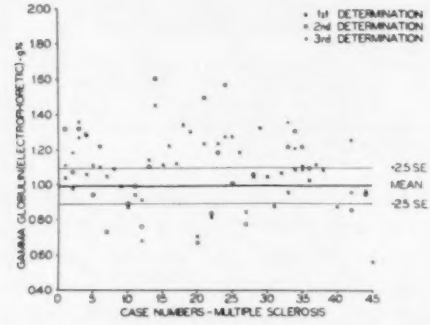


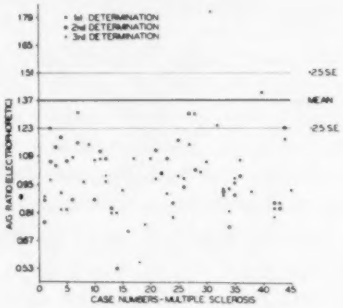
Fig. 4.—Scattergram of electrophoretic serum gamma globulin fraction in 43 cases of multiple sclerosis (79 determinations), including repeat studies on the same patients performed from 2 to 24 months later.

Statistical Data: Mean = 1.11 ± 0.25 S. D.; S. E. = ± 0.03; S. T. = 2.7; Est. Range of Pop. = 1.03 to 1.19 gm. per 100 ml. The normal mean and the estimated range of the normal population are indicated in the Figure.

trated in Figure 2, shows an increase above the expected range of the normal population in 65% of the 79 determinations. For the first series of 43 cases, 58% are positive; and in the repeat study of 28 patients, 68% showed significantly increased alpha-2 globulin values. Figure 3 shows the scattergram for the beta globulin values, which are significantly increased in 66% of the 79 deter-

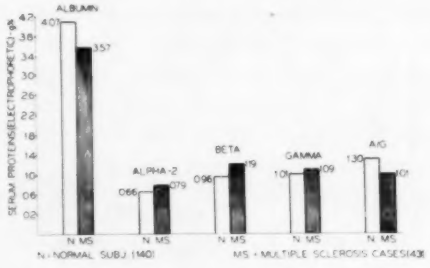
Fig. 5.—Scattergram of electrophoretic A/G ratio values in 43 cases of multiple sclerosis (79 determinations), including repeat studies on the same patients performed from 2 to 24 months later.

Statistical Data: Mean = 0.98 ± 0.25 S. D.; S. E. = ± 0.03; S. T. = 7.5; Est. Range of Pop. = 0.90 to 1.06 gm. per 100 ml. The normal mean and the estimated range of the normal population are indicated in the Figure.



minations. The first and second series of multiple sclerosis cases gave significantly increased betaglobulin serum values of 63% and 64%, respectively. The scattergram of the gamma globulin, shown in Figure 4, discloses an increase in this protein fraction in approximately 50% of the determinations performed. The A/G ratio values for the sera of the multiple sclerosis cases, as seen in Figure 5, are decreased in 90% of the 79 determinations below the expected lower limit of the normal population. Eighty-six per cent of the multiple sclerosis patients in

Fig. 6.—Mean values of electrophoretic protein fractions of 43 multiple sclerosis cases, as compared with those obtained from 140 normal subjects.



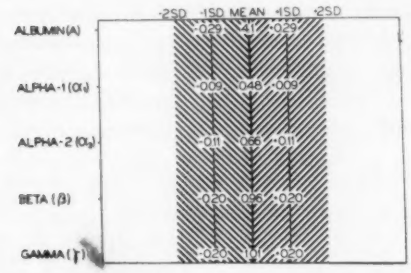


Fig. 7.—The "ideal" serogram compiled from the mean electrophoretic protein fractions of 149 normal sera (140 subjects) and the standard deviations for each fraction. The hatched area represents twice the standard deviation.

the first series and 93% in the second series also showed a decrease below this limit.

The significant electrophoretic serum protein findings, including gamma globulin, for the group of 43 multiple sclerosis cases, as compared with the mean values calculated for 149 normal sera, run under similar experimental conditions, are illustrated in Figure 6.

2. *Serograms.*—(*a*) Normal Controls: This graphic method of representing electrophoretic serum protein data has been described by us in a previous publication.[3] As can be seen in Figure 7, the "ideal" serogram corresponds to a straight line and represents the mean normal values of the 149 sera shown in the Table. Each vertical line, to the left and to the right of the mean, represents —1 S. D. and +1 S. D., respectively. The hatched area, corresponding to ±2 S.D., would contain statistically the electrophoretic values obtained in 95 out of 100 normal sera. The kind of patterns observed in healthy persons, including the repeat studies carried out on the same person, are presented in Figure 8.

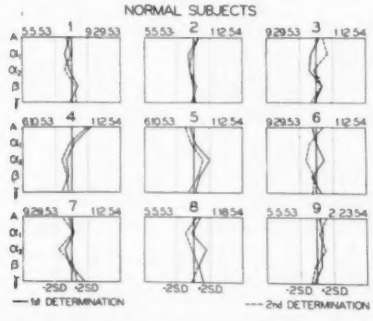


Fig. 8.—Typical serograms of nine normal subjects, including repeat studies performed from two to eight months later.

(*b*) Multiple Sclerosis Patients: Figure 9 demonstrates the serograms of nine patients with multiple sclerosis, including the results of the first and second determinations. These typical patterns indicate rather clearly the frequent decline of the albumin, as well as the corresponding increases in the alpha-2 and beta globulins, as compared with normal values, observed in most of the multiple sclerosis cases. The repeat serograms of these multiple sclerosis cases were in general agreement with the relatively unchanged clinical condition of the patients during the time interval between determinations. In those patients whose clinical status showed

Fig. 9.—Serograms of nine patients with multiple sclerosis, including repeat studies performed from 2 to 24 months later.

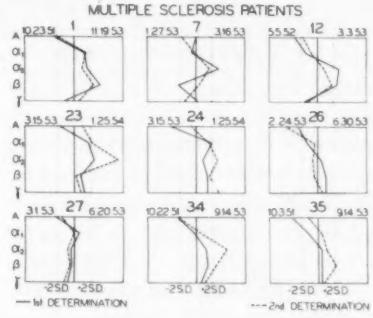
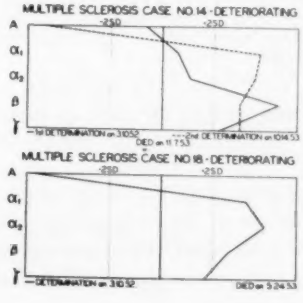


Fig. 10.—Serograms of two patients with multiple sclerosis showing rapid progressive deterioration of their clinical status. There is marked accentuation of the protein changes as compared with those usually found in this disease.



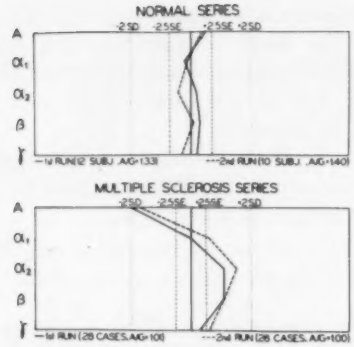


Fig. 11.—Serograms representing the means of the first and second series of normal subjects, as well as the means of the original and repeat studies of 28 multiple sclerosis patients. The albumin and alpha-2 and beta globulin fractions fall well outside the ± 2.5 S. E. limit for the multiple sclerosis cases, as compared with normals.

relatively rapid, progressive deterioration, the serograms evidenced a marked accentuation of the changes in these protein fractions. This is clearly apparent from the serograms of two patients shown in Figure 10, who died during the course of these studies and whose clinical diagnosis was confirmed at autopsy.

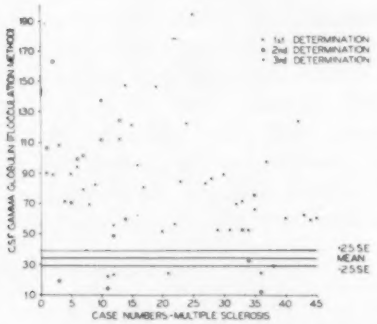


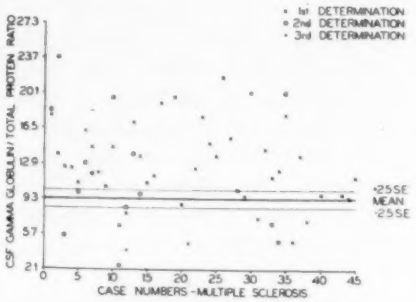
Fig. 12.—Scattergram of chemical cerebrospinal fluid gamma globulin fractions in 41 cases of multiple sclerosis (57 determinations), including repeat studies on the same patients performed from 2 to 24 months later.

Statistical Data: Mean = 7.72 ± 3.84 S. D.; S. E. = ± 0.51; S. T. = 8.0; Est. Range of Pop. = 6.45 to 9.00 mg. per 100 ml. The normal mean and the estimated range of the normal population are indicated in the Figure.

The serograms shown in Figure 11 represent the means of the first and second series of protein determinations of our normal subjects, as well as the means of the original and repeat studies of 28 patients with multiple sclerosis. It can be noted that both normal series fall well within ±2.5 standard error units (S. E.) for the electrophoretic method. On the other hand, it is clearly evident that the mean values of both the first and the second series of multiple sclerosis cases are outside the range of ±2.5 S. E. as far as the albumin and alpha-2 and beta globulin fractions are concerned. Statistically, the standard error, rather than the standard deviation, is employed for the comparison of the means of normal and disease populations.§ Therefore, a ± 2.5 S. E. limit would include approximately 99 out of 100 such normal series. The striking parallelism

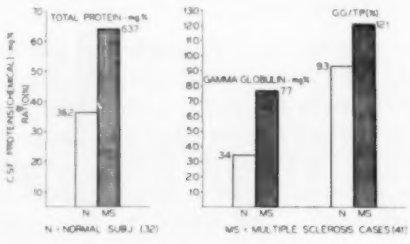
Fig. 13.—Scattergram of the chemical cerebrospinal fluid gamma globulin-total protein (G. G./T. P.) ratios in 41 cases of multiple sclerosis (57 determinations), including repeat studies on the same patients performed from 2 to 24 months later.

Statistical Data: Mean = 12.12 ± 4.93 S. D.; S. E. = ± 0.65; S. T. = 3.8; Est. Range of Pop. = 10.50 to 13.75%. The normal mean and the estimated range of the normal population are indicated in the Figure.



§ References 11 and 12.

Fig. 14.—Mean values for cerebrospinal fluid total proteins, gamma globulins, and the G. G./T. P. ratio of 41 multiple sclerosis cases, as compared with those obtained from 32 normal subjects.



in the shape of the curves for the multiple sclerosis cases is also shown in Figure 11. The dotted line in this, the lower, figure, representing the means of the second series of determinations performed one and one-half to two years (average) after the first set of values, shows a slight shift away from the normal pattern. This finding is again in keeping with the slow clinical progression of this chronic disease.

3. *Cerebrospinal Fluid.*—(*a*) Normal Subjects: Owing to the difficulties in obtaining normal cerebrospinal fluids for experimental comparison with the multiple sclerosis patients, the values for normal subjects obtained by Kabat and associates [13] were used for the statistical analysis of our own data. The estimated range of the total protein values for the normal population, according to these authors, is from 32 to 40 mg. per 100 ml. This range checks closely with the accepted normal range for the total protein method employed in our laboratory.[6] The protein flocculation-ninhydrin gamma globulin procedure [5] for cerebrospinal fluid used in these studies was checked against the more complex immunochemical method [14] in more than 100 specimens run in parallel on the same samples and was found to check within ±0.5 mg. per 100 ml. over a wide range of gamma globulin values. This close correlation of the values obtained with the two procedures for cerebrospinal fluid gamma globulin justifies the use of Kabat's normal data for our own statistical analysis. The estimated normal range of the population for cerebrospinal fluid gamma globulin varies from 2.9 to 3.9 mg. per 100 ml. and for the G. G./T. P. ratio from 8.5% to 10.2% for the 32 normal subjects.

(*b*) Multiple Sclerosis Patients: Statistical analysis of the cerebrospinal fluid data for 41 out of the 43 multiple sclerosis patients whose serum findings were previously discussed showed very significant group differences for the total protein, gamma globulin, and G. G./T. P. ratio. The estimated range of the total protein values for the multiple sclerosis population is from 57 to 70 mg. per 100 ml. (mean 64 mg. per 100 ml.), with a standard error of ±2.6. Although the mean total protein concentration of the multiple sclerosis determinations is approximately twice that of normal, no scattergrams are included in this study because these values are incorporated in the G. G./T. P. ratios. Moreover, the gamma globulin and the G. G./T. P. ratio, rather than total protein values, are considered by Kabat and his coworkers || as in best agreement with the clinical diagnosis of this disease. The scattergram of the cerebrospinal fluid gamma globulin values (Fig. 12) illustrates the increase in this fraction, in that 90% of the 57 determinations fall outside the estimated range of the normal population. Of the first series, of 41 multiple sclerosis cases, for which cerebrospinal fluids were obtained, 88% show a statistically significant increase.

The calculated values for the G. G./T. P. ratio show a significant increase above the estimated range of the normal population in 68% of the 56 determinations performed (Fig. 13). For the first series of multiple sclerosis patients (41) a similar increased ratio value (70%) was also found. Because a second spinal tap was obtained only in 14 cases, this small series was not listed separately in our calculations.

The data for the mean values of the cerebrospinal fluid total proteins, gamma globulins, and G. G./T. P. ratios for the 41 patients with multiple sclerosis, as compared with the means for 32 normals, are illustrated in Figure 14.

4. *"Protein Profile" in Multiple Sclerosis.*—The electrophoretic serum protein findings in the 43 multiple sclerosis patients indicate that only 1 showed a completely normal pattern. Of these cases, 77% disclosed a significant decrease in the albumin and A/G ratio values, a significant increase in the alpha-2 and/or beta globulins, and a normal (or slightly elevated) gamma globulin fraction. Of the 41 patients of this group on whom cerebrospinal fluid studies were performed, 93% showed either an elevated gamma

|| References 13 and 14.

globulin and/or an elevated G. G./T. P. ratio. When both the serum protein and the cerebrospinal fluid findings were combined in the "protein profile," 30 of the 41 patients (or 73%) showed significant changes in both these biological fluids.

COMMENT

In this study of 43 multiple sclerosis patients, statistically significant protein changes, as compared with those for normals, were found both in serum and in cerebrospinal fluid. For the serum, 77% of these 43 cases (Fig. 6) showed a decreased electrophoretic albumin and A/G ratio, increased alpha-2 and/or beta globulins, and a normal gamma globulin (or slightly elevated beyond the expected limits of the normal population). Of these 43 subjects, 32 were patients in this institution whose known disease process averaged 22 years, with a minimum of 6 years, as compared with the 8-year average duration, with a minimum of 2 years, for the 11 V.A. cases included in this study. Twenty-nine of these 32 long-term patients (91%) showed the characteristic serum protein findings listed above. On the other hand, only 4 of the 11 V. A. patients disclosed the typical serum protein pattern. It is interesting to note that in three of these four positive V. A. cases, the duration of the disease ranged from 9 to 11 years, and that in the remaining case the disease has lasted for 5 years. These results would imply that in multiple sclerosis the cerebrospinal fluid protein changes occur prior to those of the serum, although 7 of the 11 earlier V.A. cases showed decreased albumin values. No explanation is being offered at present for the lowered albumin values in this disease. However, increases in the alpha and beta globulins, the main lipid-carrying fractions of the blood plasma, may possibly reflect the degenerative processes of the lipid-rich myelin sheath.[15] In general, these findings confirm our previous observations[1] of the serum protein changes found in 23 long-term patients with multiple sclerosis. Furthermore, neither were any significant changes from the normal observed in the serum total protein or alpha-1 globulin values in this study. The smaller percentage of cases showing significant changes in both the alpha-2 and the beta globulins, as compared with our previous study, is due both to the larger patient material used and to the inclusion of a group of patients whose disease is of much shorter duration.

The serogram, as previously proposed by us,[3] has proved to be a most useful graphic means of presenting electrophoretic serum protein data. It is of particular practical importance in following the clinical course of a disease serially with the electrophoretic method. The reproducibility of such electrophoretic patterns for the same subjects over extended periods of time has been previously reported by Bernfeld and associates[16] for both normal subjects and patients with various diseases. This reproducibility of the general features and appearance of the patterns in one and the same person is shown by these authors through a succession of electrophoretic curves photographed on the same plate. The "serogram" method employed by us not only illustrates this high order of reproducibility of electrophoretic patterns in both normal subjects (Fig. 8) and multiple sclerosis patients (Fig. 9) over long time intervals, but also presents the serum protein data in quantitative terms, i. e., grams per 100 ml. of serum. This pictorial technique enables the clinician to determine at a glance whether the pattern is normal or abnormal and whether any significant changes occur during the course of a disease. The change of the pattern in either direction from the midline, representing the normal mean values, is apparent in comparing the serograms of the multiple sclerosis cases with those of the normal subjects (Fig. 11). It is even more evident for the serograms (Fig. 10) for patients who showed clinical signs and symptoms of rapid deterioration, leading to eventual death. Three such patients were autopsied and the clinical diagnosis of multiple sclerosis was confirmed. A further advantage of the "serogram" method for presenting serum protein data is shown in Figure 11, where the results

obtained for the mean values of the normal series are compared with those of the multiple sclerosis patients. The similarities of the patterns for the first and second series of determinations, in both normal and disease states, are also strikingly illustrated in these serograms.

The procedures used in the statistical analysis of these data and the statistical terms employed are those found in the textbooks by Fisher [11] and Mainland.[12] The means, standard deviations, standard errors, the estimated range of the normal population, and the significance of the deviations from the normal means (significance test, or S. T.) are presented in the legends under each scattergram for both the serum and the cerebrospinal fluid proteins. For the statistical analysis, only our own normal data were used, although for the serograms and graphs the mean values employed were those of the 149 normal sera whose data are given in the Table.

Perhaps the meaning of these statistical data can be most clearly represented if the values for the S. T. are projected in terms of the odds against getting the means of a similar group which is outside the probable error. For example, a S. T. value of 3 implies that the odds are 22:1 that the mean value for a particular protein fraction of a series of multiple sclerosis cases will fall within the probable error of the normal mean. If the S. T. ratio increases to 5, the odds increase to 1,300:1, and if the value becomes 7, the odds then increase to 445,000:1. The statistical analysis of our data gives S. T. ratios of 7.20 for albumin, 5.16 for alpha-2 globulins, 5.26 for beta globulins, 7.50 for the A/G ratio, and only 2.7 for the gamma globulins. Except for the last protein fraction, there is no overlap for these significant fractions between the ranges for the normal and those for the multiple sclerosis population. The serum total proteins and alpha-1 globulins have S. T. ratios of less than 3 and, therefore, give overlapping ranges between the normal and the disease state.

The S. T. ratio for the cerebrospinal fluid total proteins is 9.14; that for the gamma globulin fraction is 8.02, and that for the G. G./T. P. ratio is 3.81. In accordance with the statistical interpretation of these values, there is no overlap between the range of the normal and that of the multiple sclerosis population. The normal values used in the statistical analysis of the cerebrospinal fluid protein data in this report are those published by Kabat and associates.[13] These investigators, using their immunochemical procedure [14] for the determination of gamma globulin, stated that 85% of the 100 patients with multiple sclerosis showed either (*a*) an increased gamma globulin value or (*b*) an increased G. G./T. P. ratio in the cerebrospinal fluid. Using these criteria for our patients, we found that 93% of the 41 cases had spinal fluid changes consistent with multiple sclerosis. It is of interest that while but 90% of the long-term patients had positive spinal fluid findings, 100% of the 11 V. A. cases, with an average disease duration of but eight years, gave similar cerebrospinal fluid results.

The combined pattern of serum and cerebrospinal fluid protein findings has been termed by us the "protein profile." Kabat and associates [13] have suggested that for certain neurological disease, e. g., multiple sclerosis, the rise in the cerebrospinal fluid gamma globulin may be due in part to the formation of antibody proteins synthesized by the cells of the central nervous system. This view may account for the relatively low level of the serum gamma globulin as compared with the markedly increased cerebrospinal fluid values found for this fraction in most cases of multiple sclerosis. It would also serve to explain the interesting observation that all the patients with multiple sclerosis of relatively short duration showed positive cerebrospinal fluid findings by Kabat's criteria, whereas 90% of the cases with longer disease duration gave similar results. This would imply greater activity of cerebrospinal fluid antibody (or gamma globulin) formation in the earlier stages of the disease.

In a later report by Yahr, Goldensohn, and Kabat,[17] it was stated that of 350 patients for whom the diagnosis of multiple sclerosis had been excluded on clinical grounds, or pathological studies, 16% showed elevated spinal fluid gamma globulins. Half this group of patients with positive results had neurosyphilis, and the other 8% had "neurological diseases where there is suggestive evidence of an increased serum gamma globulin or increased permeability of the blood-brain barrier." It is in these latter cases that simultaneous determinations of the serum and cerebrospinal fluid gamma globulins are important, since elevations in the serum gamma globulins above 1.5 gm. per 100 ml. are rarely encountered in multiple sclerosis. In agreement with these workers,[17] no significant statistical differences could be found in the protein data from the 43 multiple sclerosis cases with respect to sex, duration of disease, age of onset, and veteran or nonveteran status. None of the patients studied gave a clinical picture of remission during the course of this work.

Studies are now in progress dealing with the "protein profile" in other neurological conditions, with particular attention to demyelinating diseases other than multiple sclerosis. In addition, experiments are being run on the application of the cheaper paper electrophoretic technique[18] to the study of both the serum and the cerebrospinal fluid proteins, with special attention to the lipid-containing fractions. The subfractionation of electrophoretically homogeneous protein fractions, e. g., albumin and gamma globulin, is also being carried out by already published procedures from this laboratory.[19] It is hoped not only that such work will be of diagnostic and prognostic value in cases of multiple sclerosis but that the findings may aid in the elucidation of the etiological mechanisms of the demyelinating diseases in general.

SUMMARY

Electrophoretic serum protein fractions of 43 patients with typical multiple sclerosis were studied. Simultaneous determinations of the cerebrospinal fluid total proteins, gamma globulins, and gamma globulin-total protein (G. G./T. P.) ratios were performed in 41 of these cases. The combined results of these protein changes are termed the "protein profile" of multiple sclerosis.

Of these 43 patients, 77% showed statistically a significant decrease in their electrophoretic serum albumin and A/G ratio values, concomitant with a significantly elevated alpha-2 and/or beta globulin fraction and a normal (or slightly elevated) gamma globulin value. Significantly elevated cerebrospinal fluid gamma globulin levels and/or G. G./T. P. ratios were found in 93% of the 41 patients studied. Of these 41 cases, 73% gave significant changes in both biological fluids or exhibited a positive "protein profile." Statistical analysis of both serum and cerebrospinal fluid data showed no overlap of the ranges of the normal and multiple sclerosis populations except for total protein, alpha-1, and gamma globulins.

For the purpose of following the clinical course of the disease over extended periods of time by means of serum electrophoretic patterns, a new graphic method, termed the "serogram," was devised. The average mean normal values (140 subjects) for each protein fraction is represented by a straight line. Deviations from this straight line are expressed as units of standard deviation (S. D.) for each fraction in grams per 100 ml. The reproducibility of the electrophoretic serum protein data for normal subjects is readily demonstrated by means of the "serogram." It therefore permits the rapid evaluation of serum protein changes during the clinical course of a disease either in individual cases or for the group as a whole.

In accordance with the slowly progressing course of multiple sclerosis, the serograms of the group show only a slight shift toward abnormal values on repeat studies after a time interval of one and a half to two years. However, marked accentuation of the "serogram" data was found in three patients whose clinical course deteriorated rapidly.

The patient material studied consisted of two groups: (1) 32 institutionalized patients, with an average disease duration of 22 years, and (2) 11 V. A. cases, with an average disease duration of 8 years. The characteristic serum protein pattern was found in 91% of the cases in Group 1, while only four patients of Group 2 showed this change. On the other hand, 90% of the patients in Group 1 disclosed the typical cerebrospinal fluid protein changes, as compared with 100% in the V.A. group. These findings indicate that the protein changes in the spinal fluid occur prior to those in the serum.

Studies are now in progress on the application of the "protein profile" to neurological disorders other than multiple sclerosis. It is thus hoped to obtain laboratory data useful in differentiating such diseases from multiple sclerosis, as well as in elucidating some of the etiological mechanisms of these neurological conditions.

Dr. Murray E. Margulies and Dr. Augusta Alba permitted the use of patient material from the Veterans Administration Hospital of Brooklyn for our studies; Dr. L. P. Hinterbuchner and Dr. W. R. Slade, residents in neurology, assisted in the selection and work-up of the cases from the Jewish Chronic Disease Hospital, and Mr. A. Siegelaub, statistician of the Montefiore Hospital Medical Group, made the statistical analysis of the data. Mr. Herbert Fischler assisted in preparing the photographic illustrations.

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MULTIPLE INTRACRANIAL ARTERIAL ANEURYSMS

An Analysis of Their Significance

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ALTHOUGH not considered common, multiple intracranial arterial aneurysms occur with sufficient frequency to preclude the possibility that they represent merely rare coincidental abnormalities. Dandy [1] estimated that approximately 15% of cases of intracranial aneurysms were multiple, and Hamby [2] gave some consideration to their clinical and pathologic significance. Otherwise little more than casual notice has been made of them except as occasional case reports and incidental findings in statistical analyses. Even the exhaustive tabulation of intracranial aneurysms compiled by McDonald and Korb [3] is generally limited to a listing of but one, when multiple aneurysms were present. If there was rupture of one of them, it was the one listed. Hence an analysis and review of intracranial aneurysms in terms of the significance of their multiplicity appears timely.

The earliest known reference to the subject of intracranial aneurysms was made in 1761 by Morgagni,* who described intracranial arterial dilatations, presumably due to atherosclerosis. In one of the two cases that he described the intracranial arteries of a 60-year-old man were white, hard, and thickened and showed bilateral aneurysmal dilatations of the posterior communicating arteries. Nearly 40 years later, at the turn of the 19th century, Blane [5] reported bilateral aneurysms of the internal carotid arteries in a 69-year-old woman. From that time on, cases of multiple intracranial aneurysms can be found only by searching the entire literature on this subject, for no reasonably complete bibliographic index or table of multiple intracranial aneurysms has ever been published.

In most reports of the early 19th century the descriptions are clear and precise and obviously describe as intracranial aneurysms the same lesions that are generally recognized and accepted as true aneurysms today, especially in terms of location, size, and shape. Usually these arterial protuberances have been located on the major arteries at the base of the brain, including the vertebral and basilar arteries, the internal carotid arteries, and the circle of Willis and its branching cerebral vessels. In general, such aneurysms ranged from a diameter of about 0.2 cm. up to 1.5 cm., although smaller, and occasionally much larger, aneurysms were found. The woodcuts in some of the older literature illustrate these lesions most admirably.

The incidence of additional intracranial aneurysms is difficult to determine. Many reports fail even to mention whether any of the cases had multiple lesions. Other reports, however, clearly specify or indicate the percentage of multiple aneurysms present. A compilation from this latter group, including all reports with two or more cases, has been made in Table 1. Exclusion of any series without multiple aneurysms might appear to accentuate disproportionately the importance of multiplicity. Yet it is reasonably clear that whenever extra aneurysms are not mentioned in any series, adequate awareness, appreciation or interest in them is lacking. In any event, from Table 1 there were a total of 2,237 cases of intracranial aneurysm, of which 228, slightly over 10%, were of multiple lesions.

In selecting the data for Table 1, it has been noted that many writers, either alone or with collaborators, have published more than one report on aneurysms. In such in-

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* Morgagni,[4] Bk. I, Letter IV, Case 19.

TABLE 1.—*Incidence of Multiple Aneurysms*

Case No.	Author and Reference	Aneurysms	No. Cases	Multiple Aneurysms	
				Cases	Per Cent
1	Crisp, E.: A Treatise on the Structure, Diseases and Injuries of the Blood Vessels, London, J. Churchill, 1847, pp. 165-166	3	2	1	50
2	Gull [20]	7	6	1	17
3	von Hoffmann, E.: Wien. klin. Wchnschr. **7:** 823-826; 848-850; 865-868; 884-888, 1894	76	75	1	1
4	Blackburn, I. W.: J. Comp. Neurol. **17:** 493-517, 1907	4	3	1	33
5	Wichern, H.: Deutsche Ztschr. Nervenh. **44:** 220-263, 1912	19	18	1	6
6	Reinhardt, A.: Mitt. Grenzgeb. Med. u. Chir. **26:** 432-469, 1913	12	10	1	10
7	Fearnsides, E. G.: Brain **39:** 224-296, 1916	36	31	4	13
8	Drennan, A. M.: New Zealand M. J. **20:** 324-349, 1921	12 *	8	2	25
9	Berger, W.: Virchows Arch. path. Anat. **245:** 138-164, 1923	26	19	6	32
10	Conway, J. A.: Brit. J. Ophth. **10:** 78-98, 1926	47	44	3	7
11	Parker, H. L.: Arch. Neurol. & Psychiat. **16:** 728-746, 1926	6	3	2	67
12	Bagley, C.: Arch. Surg. **17:** 39-81, 1928	5	4	1	25
13	Esser, A.: Ztschr. ges. Neurol. u. Psychiat. **114:** 208-235, 1928	9	8	1	13
14	Green, F. H. K.: Quart. J. Med. **21:** 419-432, 1928	18	14	3	21
15	Székely, K.: Beitr. gerichtl. Med. **8:** 162-177, 1928	161 *	152	8	5
16	Keegan, J. J., and Bennett, A. E.: Arch. Neurol. & Psychiat. **26:** 36-49, 1931	9	8	1	13
17	Schmidt, M.: Brain **53:** 489-540, 1931	26	23	2	9
18	Dott, N. M.: Tr. Med.-Chir. Soc. Edinburgh **112:** 219-234, 1932-1933	6	4	1	25
19	Cookson, H.: Brit. M. J. **1:** 555-558, 1933	4	3	1	34
20	Jeremy, R.: M. J. Australia **2:** 551-552, 1933	3	2	1	50
21	Tuthill, C. R.: Arch. Path. **16:** 630-642, 1933	7	6	1	17
22	Garvey, P. H.: Arch. Ophth. **11:** 1032-1054, 1934	5 *	4	1	25
23	Frazier, C. H.: Surg., Gynec. & Obst. **62:** 1-33, 1936	3	2	1	50
24	Taylor, A. B., and Whitfield, A. G. W.: Quart. J. Med. **29:** 461-472, 1936	32	31	1	3
25	Cleland, J. B.: M. J. Australia **2:** 141-142, 1937	19	18	1	6
26	Slany, A.: Virchows Arch. path. Anat. **301:** 62-71, 1938	28	26	2	8
27	Bassoe, P.: Arch. Neurol. & Psychiat. **42:** 127-133, 1939	5	2	1	50
28	O'Crowley, C. R., and Martland, H. S.: Am. J. Surg. **43:** 1-9, 1939	8	5	2	40
29	Richardson, J. C., and Hyland, H. H.: Medicine **20:** 1-83, 1941	53	40	10	25
30	Sands, I. J.: Arch. Neurol. & Psychiat. **46:** 973-1005, 1941	..	25	1	4
31	Globus, J. H., and Schwab, J. M.: J. Mt. Sinai Hosp. **8:** 547-578, 1942	15 *	13	2	15
32	Magee, C. G.: Lancet **2:** 497-500, 1943	47 *	43	4	9
33	Mitchell, N., and Angrist, A.: Ann. Int. Med. **19:** 909-923, 1943	24	23	1	4
34	Riggs, H. E., and Rupp, C.: Arch. Neurol. & Psychiat. **49:** 615-616, 1943	172	131	28	21
35	Woodhall, B., and Lowenbach, H.: South. M. J. **36:** 580-587, 1943	10	6	2	33
36	Dandy [1]	133	108	16	15
37	Courville [8]	..	85	9	11
38	Moritz, A. R., and Zamcheck, N.: Arch. Path. **42:** 459-494, 1946	..	48	6	13
39	Christianson, L. G., and Totten, R. S.: Northwest Med. **48:** 396-397, 1949	5	3	2	67
40	Hicks, S. P., and Black, B. K.: Am. Heart J. **38:** 528-536, 1949	15	14	1	7
41	Murphy, J. P.: M. Ann. District of Columbia **18:** 119-128, 1949	7	5	1	20
42	Robertson, G.: Brain **72:** 150-185, 1949	96	90	5	6
43	Suter, W.: Schweiz. med. Wchnschr. **79:** 471-476, 1949	33	26	5	19
44	Ask-Upmark, E., and Ingvar, D.: Acta med. scandinav. **138:** 15-31, 1950	..	28	1	4
45	Frankel, K.: Arch. Neurol. & Psychiat. **63:** 195-204, 1950	4	3	1	33
46	Jaeger, R.: J. A. M. A. **142:** 304-310, 1950	32	31	1	3
47	Brown, R. A. P.: Glasgow M. J. **32:** 333-348, 1951	..	148	10	7
48	Falconer, M. A.: J. Neurol., Neurosurg. and Psychiat. **14:** 153-186, 1951	52	50	2	4
49	Bassett, R. C.; List, C. F., and Lemmen, L. J.: Surg., Gynec. & Obst. **95:** 701-708, 1952	..	73	4	5
50	Dekaban and McEachern [9]	..	38	7	18
51	Hamby [2]	92	85	7	8
52	Norlén [12]	120	114	6	5
53	Black, S. P. W., and German, W. J.: J. Neurosurg. **10:** 590-601, 1953	36	35	1	3
54	Clarke, E., and Walton, J. N.: Brain **76:** 378-404, 1953	13	9	3	33
55	Dinning, T. A. R., and Falconer, M. A.: Lancet **2:** 799-801, 1953	..	250	15	6
56	Wolfe [10]	52	47	5	11
57	Bigelow, N. H.	162	135	20	15
	Total		2,237	228	10

* More than the number specified.

stances the material utilized represents only one group of cases, usually the last, or at least the most numerous, in which multiple aneurysms are mentioned. One apparent exception is made with regard to Falconer, who is recorded twice, because his data in the two reports came from different sources.

A more difficult type of appraisal was the attempt to avoid duplication of the same data when it was presented by different authors. For instance, Forbus, Walsh and King, Albright, possibly Bagley, and Dandy have all had access to, and have utilized, the files of The Johns Hopkins Hospital and have sometimes included in their reports the same cases reported by others in the group. For this reason, only the material compiled by Dandy, which was the most complete and comprehensive, has been used. When one is comparing the data of Turnbull [6] and Fearnsides, it becomes clear that they both refer to and use the same source material. Since Fearnsides' evaluation was most suitable for this study, only his work has been utilized. It is not possible to determine definitely whether overlapping occurred in the reports of Tuthill and Hamby from the Buffalo General Hospital, but it would appear that there was none. The likelihood of duplication in the data given in papers by Alpers and by Jaeger has resulted in using only the material of the latter author.

On the other hand, when cases of multiple intracranial aneurysms have been given in sufficient detail so that they could be entered in Tables 3 and 4, all recognized instances of duplication have been recorded, with notation made to that effect. Needless to say, whenever an author has reported one or more of his cases on more than one occasion, only one of the references has been cited.

Whenever possible, the probable nature and type of the aneurysm has been ascertained. For purposes of Table 1, arteriosclerotic and so-called berry, or congenital, aneurysms are considered together. Syphilitic and mycotic aneurysms, however, when so designated, have been excluded and are considered later.

One impression gained from reviewing the literature indicates that multiple aneurysms occur more frequently than they are found or reported. Undoubtedly the finding of a large ruptured aneurysm often terminates an examination of the arterial tree unless an obvious second aneurysm is close by. Only a diligent search, usually made with the possibility of other aneurysms in mind, will disclose their presence.

TABLE 2.—*Multiple Intracranial Aneurysms at Albany Hospital*

Cases with autopsy	Aneurysms	No. of Cases	Multiple Aneurysms	
			No. of Cases	Per Cent
Berry (congenital)	73	56	9	16
Arteriosclerotic	25	19	7	37
Berry and arteriosclerotic (Fig. 4)	1 (each)	1	1	100
Syphilitic	1	1	0	0
Mycotic	Many	2	1	50
Total	100*	79	18	23
Cases without autopsy	62	59	3	5
Combined total	162	138	21	15

* More than number specified.

A compilation of intracranial aneurysms from the Albany Hospital autopsy files is given in Table 2. Nearly 25% of cases of intracranial aneurysms were found to be multiple. This contrasts with the findings based on clinical data, in which a diagnosis of intracranial aneurysm was made in 59 cases and in which either the patient lived or, after death, autopsy was not done; in 3 of these multiple aneurysms were found at operation, or in only about 5%. In one other case, in which autopsy was done, however, the presence and location of two aneurysms were first

demonstrated by angiography. Rarely has the simultaneous rupture of two intracranial aneurysms been reported. In none of the Albany Hospital cases of multiple aneurysms did simultaneous rupture of two aneurysms occur.

BILATERAL ANEURYSMS

Occasionally when an aneurysm is found on one of the paired intracranial arteries at the base of the brain, its duplicate, at least as regards location, if not always size and shape, may also be encountered on the opposite side. So many instances of symmetrical bilateral aneurysms have been recorded that it is extremely unlikely that this finding is due merely to chance. Sometimes, too, one finds brief incidental mention of bilateral aneurysms, such as Russell's [7] casual observation that he had seen two cases of a symmetrical arrangement of aneurysms of the two middle cerebral arteries. Courville [8] also has noted that when an aneurysm is present at a primary or secondary bifurcation of one middle cerebral artery, a second aneurysm, of variable size, may not infrequently be encountered at the same point on the other side. Scattered statistical data are also available, but cumulative study or analysis of these symmetrical aneurysms has never been undertaken. Consequently, special mention of this aspect of multiple intracranial aneurysms is warranted.

Although there are only a few reports concerning the incidence of bilateral symmetrical aneurysms in the group of multiple aneurysms, the evidence presented would indicate that the percentage is significantly high. Thus, of eight patients with multiple aneurysms in Hamby's [2] series, there were four who had bilateral symmetrical aneurysms. There appear to have been at least 9 instances of similar bilateral aneurysms among the 16 cases of multiple aneurysms in Dandy's [1] series. Three such bilateral aneurysms were present in the seven cases of multiple aneurysms recorded by Dekaban and McEachern.[5] One of Drennan's two instances of multiple aneurysms was bilateral. Suter had one case in five of multiple aneurysms; Norlén, one in six; Falconer, one in two; Robertson, one in five; Dial and Maurer, one in two, and Berger, two in six. In the Albany Hospital series there were 8 instances of bilateral symmetrical aneurysms among the group of 17 multiple aneurysms. From these figures one obtains a total of 32 in 76 cases, which is approximately 42%.

Frequently the term "bilaterally symmetrical" is used to imply similarity in size, and sometimes in shape, as well as similarity of location, so that such aneurysms are virtual mirror images of each other. Yet even if there is considerable variation in size or shape, a symmetry with regard to location represents a striking phenomenon worthy of emphasis. Therefore bilateral symmetry, as employed in Table 4, refers only to location, and not to size or shape. To be sure, many of these aneurysms were noted as being of the same size, but similarity in location only was considered the essential criterion of symmetry.

The precise similarity of location is striking when certain vessels, such as the internal carotid artery, are considered. Hamby,[2] for instance, noted that bilateral symmetry involved the subclinoid portion in two cases and the supraclinoid portion in another. Other authors have also sharply localized internal carotid aneurysms. Consequently, an observation of bilateral symmetry seldom represents merely a rough estimate (Fig. 1).

Of these 48 tabulated cases of bilateral aneurysms, some 17 represented dilatation explainable largely on the basis of arteriosclerotic degeneration of the vessel walls. Bilateral fusiform dilatations, which may form large ovoid, or even spherical, swellings of the vessel wall, are not unique in the intracranial arteries, since they may occur elsewhere in the body. Thus, the common iliac arteries just below their bifurcation from the aorta not infrequently exhibit large fusiform swellings as a result of atherosclerosis. Similarly, the cervical portions of the internal carotid arteries may show symmetrical fusiform atherosclerotic swellings, as noted by Riddler [10] and by Meyer.[11] The latter observed 3 instances of bilateral aneurysm of

the cervical portion of these arteries in a group of 11 aneurysms of the internal carotid arteries. Dempsey [12] cites Guthrie as having had a case of bilateral aneurysm of the ophthalmic arteries.

In all likelihood, then, fusiform and symmetrical dilatations of the large paired intracranial arteries at the base of the brain are frequently observed and are considered merely incidental to cerebral arteriosclerosis. Only those swellings which terminate in rupture, which cause specific neurologic symptoms, or which lead to other types of intracranial impairment are likely to be given special attention and study. At the present time there seems to be no reason to consider

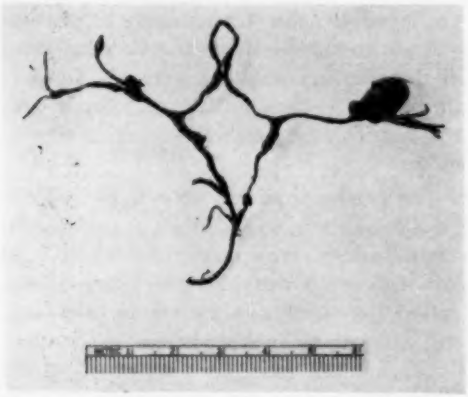


Fig. 1.—Symmetrical bilateral aneurysms of middle cerebral arteries. Partial surgical occlusion of the aneurysm on the left was performed prior to death. The larger aneurysm, on the right, had been asymptomatic.

bilateral arteriosclerotic aneurysms of the intracranial arteries as unique or unusual types of atherosclerotic degeneration.

Bilateral symmetrical aneurysms of the berry type, on the other hand, might well represent a fruitful source for investigation into the still unsettled subject concerning the etiology and pathogenesis of these lesions. Generally only one of these symmetrical aneurysms ruptures, although rupture of both symmetrical berry-type aneurysms of the anterior cerebral arteries was noted in one of the cases of Mitchell and Angrist. As Table 4 indicates, in some instances the source of bleeding may originate in one of the symmetrical aneurysms, or a third aneurysm, elsewhere, may be the source of bleeding. Occasionally such aneurysms produce no clinical symptoms and represent only an incidental postmortem curiosity.

CLINICAL IMPLICATIONS

With the advent of angiography, roentgenographic demonstration of multiple aneurysms has frequently been made, and the desirability and advisability of bilateral carotid angiography has frequently been advocated in order to ascertain their presence.† Before the advent of angiography only a few instances of multiple aneurysms were recognized in x-ray films of the skull by means of abnormal calcification in the aneurysms.‡ Scott, on the basis of rather bizarre neurologic findings, suggested a clinical diagnosis of multiple intracranial aneurysms.§

The immediate prognosis and eventual outcome of patients with multiple aneurysms is also of interest. As mentioned previously, only rarely do two of these lesions rupture simultaneously.‖ However, several reports mention the leakage or rupture of a second aneurysm at some period subsequent to bleeding from an earlier one.¶ Such a situation, of course, can only occur if a person recovers from the effects of a first aneurysm. However, if there is initial survival, either with or without surgical intervention, the possibility that a second aneurysm might become symptomatic needs to be kept in mind, especially if its presence has been clinically demonstrated. In passing, it is to be noted that there are a number of reports in which it was believed that a leaking aneurysm which had temporarily healed gave rise to a second episode of bleeding a number of years later. Rosen and Kaufmann reported a case with a symptom-free interval of 27 years between initial and final rupture.[17]

† References 9 and 13.

‡ References 1 and 14.

§ Scott, M., in discussion on Wycis.[15]

‖ Table 3, Cases 42 and 72; Table 4, Case 37.

¶ Wolfe.[16] Table 3, Cases 16, 91, 110, 134; Table 4, Case 51.

TABLE 3.—*Individual Cases of Multiple Aneurysms*

Case No.	Author and Reference	Age	Sex	Aneurysms	Probable Type *	Site †	Comment
1	Kingston, P. N.: Edinburgh M. & S. J. **57:** 69-77, 1842	14	M	2	..	I. C., Ba	Carotid aneurysm, partly extracranial
2	Thomson, A. T.: London & Edinburgh Month. J. M. Sc. **2:** 557-563, 1842	49	M	3	A	I. C.,‡ I. C.	Third aneurysm of opposite I. C.; basilar artery dilated; circle of Willis incomplete
3	Crisp, E.: A Treatise on the Structure, Diseases and Injuries of the Blood Vessels, London, J. Churchill, 1847, p. 165-166	14	M	2	B	R. A. C.,‡ R. A. C.	.....
4	Bowen, W. S.: New York J. Med. **13:** 345-348, 1849	33	M	2	..	Ba,‡ R.V.	.....
5	Bristowe: Tr. Path. Soc., London **10:** 3-4, 1858-1859	60	F	3	A	L. M.C.,‡ A. Com.,‡ Ba	.....
6	Gull [29]	30	F	2	..	L. M. C.,‡ L. M. C.	.....
7	Ogle, J. W.: Brit. & Foreign Med. Rev. **36:** 491-521, 1865	..	..	2 §	..	M. C., V.‖	Museum specimen
8	Lepine, R.: Gaz. méd., Paris **22:** 700-704, 1867	78	F	2	..	R. M. C.,‡ R. M. C.	.....
9	Bourneville: Bull. Soc. anat., Paris **43:** 449-453, 1868	53	F	5	A	R. M.C., L. P. C.,‡ R. P. C., R. V.	P. C. aneurysms symmetrically located; also miliary aneurysms, 3 on gyri and 1 on corpus striatum
10	Russell: Brit. M. J. **2:** 87-89, 1870	26	M	2	S (?)	R. M. C., Ba	Syphilitic etiology not clearly established
11	Sevestre: Bull. Soc. anat., Paris **47:** 415-420, 1872	45	M	2	A	L. V.,‡ L. V.	.....
12	MacSwiney: Dublin J. M. Sc. **59:** 373-375, 1875	60	F	2 §	A	Branches of Ba	Ruptured aneurysm sup. cerebellar art.
13	Griesinger (cited by Peacock, T. B.: St. Thomas's Hosp. Rep. **7:** 119-177, 1876)	56	M	2	A	Ba., L. V.	.....
14	Gueniot (cited by Peacock)	47	F	2	A	Ba., L. V.	.....
15	Barlow, T.: Tr. Path. Soc., London **29:** 8-9, 1878	52	M	5	A	Branch of A. C.‡	Four small (miliary) aneurysms on adjacent small vessels; anomalous circle of Willis
16	Glover, J. G.: Lancet **1:** 539, 1883	..	F	2	..	I.C.,‡ I. C.	Apparent rupture of other aneurysm nine years before
17	Eppinger,[32] p. 87	23	M	9	B	L. M. C., 7 Ba	Ruptured aneurysm l. profunda (? art. femoris)
18	Watson, T. A.: Lancet **2:** 718, 1888	53	F	2	A	M. C., Ba	Bilateral optic atrophy, from pressure on chiasm by M. C.
19	von Hofmann, E.: Wien. klin. Wchnschr. **7:** 867-868; 886-888, 1894	36	M	2	..	L. A. C.,‡ L. A. C.	.....
20	Shaw, B. H.: J. Ment. Sc. **47:** 547-548, 1901	50	F	2	A	R. I. C., R. M. C.‡	.....
21	Blackburn, I. W.: J. Comp. Neurol. **17:** 493-517, 1907 (Case 2163)	68	M	2	..	R. I. C., R. A. C.	Anomalous circle of Willis
22	Wichern, H.: Deutsche Ztschr. Nervenh. **44:** 220-263, 1912 (Case 19)	56	F	2	S (?)	P. C.,‡ Ba	Syphilitic arteritis said to be present
23	Reinhardt, A.: Mitt. Grenzgeb. Med. u. Chir. **26:** 432-469, 1913 (Case 5)	72	F	3	A	R. M.C.,‡ R. P. Com., Ba	.....
24	Roberts, W. H.: Tr. Am. Laryng., Rhin. & Otol. Soc. **19:** 442, 1913	..	F	2	A	R. I. C.,‡ Ba	.....
25	Fearnsides, E. G.: Brain **39:** 224-296, 1916 (Case 3)	60	M	2	A	R. M. C.‡ R. M. C.	.....
26	Fearnsides, Case 4	49	F	2	A	R. I. C., L. A. C.‡	.....
27	Fearnsides, Case 11	53	M	2	..	R. M. C., L. A. C.	Polycystic kidneys
28	Fearnsides, Case 26	36	F	3	A	R. I. C.,‡ 2 R. M. C.	.....
29	McMullin, J. J. A.: U. S. Nav. M. Bull. **12:** 702-704, 1918	54	M	2	S (?)	L. P. C.,‡ P. C.	Syphilitic aortitis present

TABLE 3.—*Individual Cases of Multiple Aneurysms*—Continued

Case No.	Author and Reference	Age	Sex	Aneurysms	Probable Type *	Site †	Comment
30	Drennan, A. M.: New Zealand M. J. **20:** 324-349, 1921 (Case 7)	46	F	2 §	A	M. C.‖ A. Com.‡	.....
31	Berger, W.: Virchows Arch. path. Anat. **245:** 138-164, 1923 (Case 5)	70	F	2	A	L. M. C.,‡ L. M. C.	Rupture of more distal aneurysm
32	Berger, Case 13	56	F	2	A	R. I. C., R. P. Com.	Rupture mid. cerebral artery, which had no aneurysm
33	Berger, Case 16	50	F	3	A	L. I. C., R. I. C., Ba	Left carotid aneurysm saccular; others fusiform
34	Berger, Case 17	45	F	2	A	L. I. C.,‡ L. I. C.	.....
35	Katz, G., and Mühe, E.: Ztschr. Urol. **18:** 453-461, 1924	45	F	2	..	R. I. C., A. Com.‡	Polycystic kidneys
36	Conway, J. A.: Brit. J. Ophth. **10:** 78-98, 1926	23	M	2	B	R. M. C.,‡ P. Com.	Ruptured aneurysm, berry type; other one fusiform
37	Conway	50	M	2	A	L. M. C.,‡ R. M. C.	.....
38	Conway	old	M	2	..	L. M. C.,‡ A. C.	.....
39	Parker, H. L.: Arch. Neurol. & Psychiat. **16:** 728-746, 1926	20	M	2	B	A. Com., P. Com.‡	Coaretation of aorta; P. Com. aneurysm at junction with M.C. (P. Com. usually originates from I. C.); same as case 43, (Woltman and Shelden)
40	Symonds, C. P.: Clin. J. **55:** 217-221, 1926	..	M	2	..	L. M. C., R. A. C.‡	.....
41	Globus, J. H., and Strauss, I.: Arch. Neurol. & Psychiat. **16:** 215-239, 1927	68	M	s	A		Posterior inferior cerebellar artery
42	Sands, I. J., and Lederer, M.: J. Nerv. & Ment. Dis. **65:** 360-371, 1927 (Case 3)	31	M	2	..	2 L. P. Com.‡	Rupture of both aneurysms
43	Woltman, H. W., and Shelden, W. D.: Arch. Neurol. & Psychiat. **17:** 303-316, 1927	20	M	2	B	A. Com., P. Com.‡	Coaretation of aorta; same as Case 39 (Parker)
44	Bagley, C.: Arch. Surg. **17:** 39-81, 1928 (Case 4)	37	M	2	B	L. A. C.,‡ L. A. C.	Rupture of more distal aneurysm
45	Eppinger (cited by Abbott, M. E.: Am. Heart J. **3:** 574-618, 1928)	17	M	2	..	L. A. C., R. A. C.‡	Coaretation of aorta, bicuspid aortic valves
46	Esser, A.: Ztschr. ges. Neurol. u. Psychiat. **114:** 208-235, 1928 (Case 5)	67	F	2 §	A	V.‖	.....
47	Green, F. H. K.: Quart. J. Med. **21:** 419-432, 1928 (Case 3)	21	M	4	B	R. A. C.,‡ R. A. C., Ba, L. V.	Coaretation of aorta, bicuspid aortic valves
48	Newman, S. H.: Southwestern Med. **12:** 408, 1928	32	M	7 §	S (?)	Ba,‡ 6-7, Ba	4+ Wassermann reaction of spinal fluid; aneurysms considered syphilitic by author
49	Székely, K.: Beitr. gerichtl. Med. **8:** 162-177, 1928 (Case 2)	64	M	2	..	R. M. C., L. M. C.	In all cases, rupture of at least one aneurysm
50	Székely, Case 12	78	F	2 §	..	A. Com.‖	.....
51	Székely, Case 29	36	F	2	..	2 A. Com.	.....
52	Székely, Case 33	51	M	2	..	A. Com., L. V.	.....
53	Székely, Case 46	54	F	2	A	L. M. C., R. M. C.	.....
54	Székely, Case 70	62	F	2	A	3 R. M. C.	.....
55	Székely, Case 121	36	M	2	..	Ba, L. V.	.....
56	Székely, Case 127	25	F	2 §	..	R. M. C.‖	.....
57	Forbus, W. D.: Bull. Johns Hopkins Hosp. **47:** 239-284, 1930	24	M (C)	5	B	2 L. M. C., L. A. C., R. A. C.‡	Site of 5th aneurysm unspecified; Case 94 (Dandy)
58	Helpern, M.: Arch. Path. **16:** 754-756, 1933	51	M	3	B	L. I. C.,‡ R. M. C. A. C.	.....
59	Jeremy, R.: M. J. Australia **2:** 551-552, 1933 (Case 2)	47	F	2	..	L. A. C.,‡ P. C.	.....
60	Tuthill, C. R.: Arch. Path. **16:** 630-642, 1933 (Case 1)	39	F	2	A?		Rupture vessel near medulla; aneurysm of meningeal vessel over cerebellum, of miliary type (?)

TABLE 3.—*Individual Cases of Multiple Aneurysms*—Continued

Case No.	Author and Reference	Age	Sex	Aneurysms	Probable Type *	Site †	Comment
61	Garvey, P. H.: Arch. Ophth. **11:** 1032-1054, 1934 (Case 4)	64	F	2 §	A	R. I. C.,‡ M. C.‖	.....
62	Kersley, G. D.: Brit. M. J. **1:** 376-377, 1934	38	F	2	B	L. M. C.,‡ L. M. C.	Antepartum hemorrhage; B. P. 215/140
63	Manger, W.: Canad. M. A. J. **33:** 401-403. 1935	35	M	3	A	R. I. C., 2 Ba	Large aneurysms measured 3.0, 3.0, 1.25 cm., respectively in greatest dimensions
64	Taylor, A. B., and Whitfield, A. G. W.: Quart. J. Med. **29:** 461-472, 1936	59	F	2	..	.....	Two unruptured aneurysms of circle of Willis, omitted from author's series
65	Cleland, J. B.: M. J. Australia **2:** 141-142, 1937	54	M	2	..	.....	One aneurysm size of walnut
66	Dial, and Maurer,[47] Case 10	49	M	3	S (?)	3 R. M. C.	Dementia paralytica; arteritis in aneurysm, possibly syphilitic
67	Karmally, A., and Manohar, K. D.: Brit. M. J. **2:** 962-963, 1937	30	M	2	..	L. M. C., A. Com.	.....
68	Maass, U.: Beitr. path. Anat. **98:** 307-322, 1937	69	F	2	S	R. M. C.,‡ A. Com.	Photomicrograph of syphilitic arteritis with aneurysm formation
69	Nevin, S., and Williams, D. J.: Lancet **2:** 955-958, 1937	45	F	4	(?) B or A	2 L. I. C., L. M. C., L. A. C.	Died of ruptured aneurysm of splenic artery; anomalous circle of Willis
70	Courville, C. B., and Olson, C. W.: Bull. Los Angeles Neurol. Soc. **3:** 1-21, 1938 (Case 5)	38	M (C)	2	..	R. M. C., A. Com.‡	.....
71	Courville, Case 8	42	M	2	..	R. A. C.,‡ A. Com.	Ruptured aneurysm just distal to intact one
72	Courville, Case 19	55	M	2	..	R. M. C.,‡ A. Com.‡	Simultaneous rupture of 2 aneurysms
73	Slany, A.: Virchows Arch. path. Anat. **301:** 62-71, 1938	48	F	2	..	L. M. C.,‡ R. M. C.	Anomalous circle of Willis
74	Slany	56	F	2	..	L. M. C., R. M. C.‡	Anomalous circle of Willis
75	Walker, J. B., and Livingstone, F. D. M.: Lancet **2:** 660-663, 1938	17	M	2 §	B	L. V.‖	Coaretation of aorta; subarachnoid hemorrhage, probably due to rupture of one of aneurysms; anomalous circle of Willis
76	Bassoe, P.: Arch. Neurol. & Psychiat. **42:** 127-133, 1939	31	F	4	S (?)	2 Ba, L. V.	Fourth aneurysm in brain stem thought syphilitic in etiology but no evidence of syphilitic arteritis
77	Evans, N. G., and Courville, C. B.: Bull. Los Angeles Neurol. Soc. **4:** 145-167, 1939	..	..	3	..	L. M. C., R. M. C., A. Com.	Photograph of lesions; M. C. aneurysms, may be symmetrical
78	O'Crowley, C. R., and Martland, H. S.: Am. J. Surg. **43:** 1-9, 1939	42	M	3	B	2 L. M. C., R. M. C.‡	Polycystic kidneys, also cystic liver and spleen
79	O'Crowley and Martland	20	M	2	B	R. M. C.,‡ L. V.	Congenital hypoplasia left kidney
80	Hermann, K., and Macgregor, A. R.: Brit. M. J. **1:** 523-525, 1940	4½	M	2	B	A. C.,‡ A. C.	Unruptured aneurysm 1.0 cm. posterior to ruptured one (i. e., close to circle of Willis)
81	Richardson, J. C., and Hyland, H. H.: Medicine **20:** 1-83, 1941	49	F	2	B	A. Comp.,‡ P. Com.	.....
82	Sands, I. J.: Arch. Neurol. & Psychiat. **46:** 973-1005, 1941	42	F	2	..	L. I. C.,‡ A. Com.	.....
83	Globus, J. H., and Schwab, J. M.: J. Mt. Sinai Hosp. **8:** 547-578, 1942 (Case 3)	56	M	2	..	R. A. C.,‡ A. Com.	.....
84	Globus, and Schwab (Case 5)	59	F	‖	..	.....	Intracerebral cystic hematomas enclosed by vascular walls without demonstrable relationship to arteries

TABLE 3.—*Individual Cases of Multiple Aneurysms*—Continued

Case No.	Author and Reference	Age	Sex	Aneurysms	Probable Type *	Site †	Comment
85	Walsh, F. B., and King, A. B.: Arch. Ophth. **27:** 1-33, 1942	58	M	3	..	L. M. C., R. M. C., Ba	Coaretation of aorta
86	Walsh, and King	59	F	3	..	A. Com.,‡ Ba	Third aneurysm on posterior inferior cerebellar artery
87	O'Reilly, J. N., and Chapman, O. W.: Arch. Dis. Childhood **18:** 109-111, 1943	13	M	2	B	A. Com.‡	Coaretation of aorta; 2d aneurysm of left choroidal art.
88	Woodhall, B., and Lowenbach, H.: South. M. J. **36:** 580-587, 1943 (Case 3)	38	F (C)	4	B	R. I. C.	Three other aneurysms in region of circle of Willis
89	Woodhall, and Lowenbach, Case 5	49	M	2	B	L. M. C., R. A. C.‡	.....
90	Dandy,[1] Table B-XXIV	68	F	3	..	I. C., M. C., Ba	.....
91	Dandy,[1] Table B-XXIX	36	F	3	B	R. I. C., A. Com.	Ruptured aneurysm rt. ant. choroidal; hemorrhage from A. com. aneurysm 5 mo. earlier
92	Dandy,[1] Table B-XXX	62	F	2	B	L. I. C., A. Com.	.....
93	Dandy,[1] Table C-II	24	M (C)	4	B	3 L. M. C., R. A. C.‡	Same as Case 58 (Forbus)
94	Dandy,[1] Table C-XXI	52	F	2	B	R. A. C.	Rupture post. inf. cerebellar artery aneurysm
95	Dandy,[1] Table C-XXII	53	M	3	B	L. I. C.,‡ R. A. C., P. C.	Rupture of aneurysm in cavernous sinus formed A-V fistula
96	Dandy,[1] Table G-XIII	63	F	2	A	Ba, L. V.	.....
97	Aring, C. D.: Dis. Nerv. System **6:** 119-124, 1945, Case No. 44-2976	30	F	3	..	L. I. C., A. Com., Ba	Massive intracranial cavernous angioma (?A-V aneurysm)
98	Moritz, A. R., and Zamcheck, N.: Arch. Path. **42:** 459-494, 1946	38	M	2	A	R. I. C.,‡ L. I. C.	.....
99	Edwards, J. E.; Christensen, N. A.; Clagett, O. T., and McDonald, J. R.: Proc. Staff Meet., Mayo Clin. **23:** 324-332, 1948	28	M	2	B	L. I. C., A. Com.	Coaretation of aorta, bicuspid aortic valves; photograph of circle of Willis
100	Alpers, B. J., and Schlezinger, N. S.: Arch. Ophth. **42:** 353-364, 1949 (Case 7)	58	F	2	..	R. M. C., R. P. Com.‡	.....
101	Christianson, L. G., and Totten, R. S.: Northwest Med. **48:** 396-397, 1949 (Case 1)	47	M	2	..	R. I. C., M. C.	Apparent rupture of mid. cerebral on right
102	Christianson, and Totten, Case 2	39	M	2	..	R. M. C., Ba ‡	.....
103	Hicks, S. P., and Black, B. K.: Am. Heart J. **38:** 528-536, 1949	27	M	2	..	M. C., A. C.‡	Hypertension 4 yr.; heart weighed 500 gm.
104	Murphy, J. P.: M. Ann. District of Columbia **18:** 119-128, 1949 (Case 4)	36	M	3	..	L. I. C., L. A. C., A. Com.	Aneurysms seen on angiograms
105	Suter, W.: Schweiz. med. Wchnschr. **79:** 471-476, 1949 (Case 3)	73	M	3	..	L. M. C., R. M. C., R. A. C.	Diabetic coma
106	Suter, Case 7	41	F	2	..	2 L. I. C.	.....
107	Suter, Case 8	55	F	2	..	R. P. Com., R. P. C.‡	.....
108	Suter, Case 19	34	M	2	..	R. I. C.,‡ A. Com.	.....
109	Frankel, K.: Arch. Neurol. & Psychiat. **63:** 195-204, 1950 (Case 1)	58	F	2	..	R. M. C., R. P. Com.‡	.....
110	Hyland, H. H.: Arch. Neurol. & Psychiat. **63:** 61-78, 1950	44	F	2	B	L. I. C.,‡ R. M. C.	Middle cerebral aneurysm bled 3 yr. earlier
111	Sahs, A. L.: Arch. Neurol. & Psychiat. **63:** 524, 1950	26	..	6	..	L. I. C.‡	Five other aneurysms at arterial bifurcations; polycystic kidneys
112	Bassett, R. C.: J. Neurosurg. **8:** 132-133, 1951	30	M	2	..	R. I. C.,‡ R. M. C.	.....
113	Brown, R. A. P.: Glasgow M. J. **32:** 333-348, 1951	43	M	2	B	R. M. C.,‡ A. Com.	Polycystic kidneys

TABLE 3.—*Individual Cases of Multiple Aneurysms*—Continued

Case No.	Author and Reference	Age	Sex	Aneurysms	Probable Type *	Site †	Comment
114	Brown, R. A. P.: Glasgow M. J. **32:** 333-348, 1951	61	F	2 §	B	L. M. C.,‡ R. M. C.,§ A. Com.	Polycystic kidneys
115	Falconer, M. A.: J. Neurol., Neurosurg. & Psychiat. **14:** 153-186, 1951	..	..	2	..	I. C.	.....
116	Falconer	..	..	2	..	M. C.	.....
117	Poppen, J. L.: J. Neurosurg. **8:** 75-102, 1951 (Case 5)	48	F	2	..	L. I. C., R. I. C.	Demonstrated by angiograms, aneurysm on right seen 4 yr. earlier
118	Bassett, R. C.; List, C. F., and Lemmen, L. J.: Surg., Gynec. & Obst. **95:** 701-708, 1952	..	..	2	..	R. I. C., R. M. C.	.....
119	Black, S. P. W., and German, W. J.: J. Neurosurg. **10:** 590-601, 1953	34	F	2	..	R. I. C., R. M. C.‡	.....
120	Clarke, E., and Walton, J. N.: Brain **76:** 378-404, 1953 (Case 3)	45	M	3	..	L. M. C.,‡ R. M. C., A. Com.	.....
121	Clarke and Walton, Case 9	42	F	2	..	L. M. C., R. A. C.‡	.....
122	Clarke and Walton, Case 11	50	F	2	..	R. M.C.,‡ R. M. C.	.....
123	Hamby, W. B.: J. Neurosurg. **10:** 35-37, 1953	..	..	3	..	2 L. M. C., R. M. C.	Both L. M. C. aneurysms seen by angiograms
124	Bigelow, N. H. (Albany Hospital)	51	M	2	B	R. M. C., R. P. Com.‡	.....
125	Bigelow	75	F	2	A	L. I. C., R. M. C.	.....
126	Bigelow	41	M	2	B	L. M. C.,‡ Ba	.....
127	Bigelow	78	M	2	A	L. I. C., Ba	.....
128	Bigelow	52	F	10	B	.....	Anomalous circle of Willis (Case 1)
129	Bigelow	52	M	2	B	R. M. C., R. A. C.	Polycystic kidneys
130	Bigelow	47	M	2	..	A. Com.,‡ R. V.	Ruptured aneurysm of berry type but arteriosclerotic of vertebral (Fig. 5)
131	Bigelow	44	F	2	B	R. I. C.,‡ L. A. C.	.....
132	Bigelow	34	F	2	B	L. M. C., A. Com.‡	Anomalous circle of Willis
133	Bigelow	50	M	2	B	A. Com.‡ A. Com.	Coaretation of aorta, bicuspid aortic valve, anomalous circle of Willis
134	Bigelow	53	M	2	A	R. A. C., A. Com.‡	Had subarachnoid hemorrhage 3 yr. previously
135	Bigelow	47	F	2	B	L. A. C.,‡ L. A. C.	Anomalous circle of Willis

† L. indicates left; R., right; I. C., internal carotid; M. C., middle cerebral; A. C., anterior cerebral; A. Com., anterior communicating; P. Com., posterior communicating; P. C., posterior cerebral; Ba, basilar; V., vertebral artery.
* A means arteriosclerotic; B, berry or congenital aneurysm; S, syphilitic.
‡ Site of bleeding or rupture.
§ More than number specified.
‖ Several, number unspecified.

They also cited other cases with periods between episodes of from 2 to 55 years. Usually recurrent episodes of aneurysmal bleeding occur within a short time after the first one. Hence it is not only possible but probable that hemorrhage years after a first episode represents leakage from a second aneurysm rather than a recurrence of bleeding from the first.

ASSOCIATION WITH OTHER DISORDERS

As would be expected, other pathologic processes are frequently present in persons with intracranial aneurysms. While many of these are clearly coincidental, some lesions have occurred in association with intracranial aneurysms more frequently than seems possible on the basis of chance alone. For instance, as disclosed in this study, the presence

TABLE 4.—*Symmetrical Bilateral Intracranial Aneurysms*

Case No.	Author and Reference	Age	Sex	Probable Type *	Site	Comments
1	Morgagni [4]	60	M	A	P. Com.	First reported case of intracranial aneurysm
2	Blane [5]	69	F	A	I. C. (carotid canal)	.....
3	Hodgson, J.: Traité des maladies des artères et des veines, Paris, Gabon, 1819	..	..	A	V.	Museum specimen
4	Bastain, H. C.: Tr. Path. Soc. London **20:** 106-109, 1869	50	F	A	M. C.	Rupture of right, a third aneurysm in region left corpus striatum
5	Echeverria, M. G.: On Epilepsy, New York, W. Wood & Co., 1870	67	M	A	V.	Rupture of left
6	Carpenter, W. M.: M. Rec. **20:** 354-355, 1881	30	M	L	V.	.....
7	Pitt, G. N.: Brit. M. J. **1:** 827-832, 1890	18	M	M?	M. C. (1st branch)	Rupture of right; mycotic etiology doubtful
8	Ruston, W. D., and Southard, E. E.: Boston M. & S. J. **154:** 312-314, 1906	69	F	A	V.	Many miliary aneurysms of minute cortical and ganglionic arterioles
9	Heur, G. J., and Dandy, W.: Bull. Johns Hopkins Hosp. **26:** 311-322, 1916	29	M	B	I. C. (carotid canal)	Massive aneurysms seen on roentgenograms, verified by autopsy (Dandy [1] Table A-1)
10	Drennan, A. M.: New Zealand M. J. **20:** 324-349, 1921 (Case 8)	27	F	B	M. C. (1st branch)	Ruptured aneurysm A. Com.
11	Morrow, J. F.: M. Rec. **100:** 894-895, 1921	C. 50	M	A	V.	.....
12	Raeder, O. J.: Arch. Neurol. & Psychiat. **5:** 270-282, 1921	59	M	A	V., also post. cerebellar	Many intracerebral miliary aneurysms of dissecting type
13	McCordock, H. A.: Bull. Buffalo Gen. Hosp. **1:** 87-91, 1923	55	F	A	I. C.	Rupture 3d aneurysm R. P. com.
14	Sosman, M. C., and Vogt, E. C.: Am. J. Roentgenol. **15:** 122-134, 1926	62	F	A	I. C. (intracranial)	Noted on roentgenogram
15	Parker, H. L.: Arch. Neurol. & Psychiat. **16:** 728-746, 1926	21	M	..	I. C. (carotid canal)	Rupture of right, also aneurysm of basilar; anomalous circle of Willis
16	Shore, B. R.: Arch. Path. **6:**181-195, 1928	57	F	A	I. C. (intracranial)	Two unruptured fusiform aneurysms also on basilar
17	Albright, F.: Bull. Johns Hopkins Hosp. **44:** 215-245, 1929	33	M	B	M. C.	Rupture of left; Cases 18 (Forbus) and 43 (Dandy)
18	Forbus, W. D.: Bull. Johns Hopkins Hosp. **47:** 239-284, 1930	32	M	B	M. C. (at I. C.)	Rupture of left, 3d aneurysm branch L. M. C.; Case 17 (Albright) and Case 43 (Dandy)
19	Keegan, J. J., and Bennett, A. E.: Arch. Neurol. & Psychiat. **26:** 36-49, 1931	29	F (C)	B	I. C. (intracranial)	Rupture of right
20	Dott, N. M.: Tr. Med.-Chir. Soc. Edinburgh **112:** 219-234, 1932-1933	47	F	B	I. C. (intracranial)	Rupture of third aneurysm of L. I. C. at P. Com.
21	Cabot Case 19152: New England J. Med. **208:** 800-802, 1933	20	F	B	M. C. (at ant. choroidal)	Rupture of aneurysm on right
22	Cookson, H.: Brit. M. J. **1:** 555-558, 1933	58	M	B	I. C. (at M. C.)	Rupture of aneurysm on left; anomalous circle of Willis
23	Berger, W.: Virchows Arch. path. Anat. **245:** 138-164, 1933 (Case 8)	69	F	A	P. Com.	Rupture of left
24	Berger (Case 11)	70	F	A	M. C.	.....
25	Friedrich, G.: Zentralbl. Chir. **61:** 1586-1592, 1934	58	F	T (?)	I. C. (carotid canal)	Vessels arteriosclerotic; traumatic etiology doubtful
26	Thomas, F.: Ann. anat. path. **13:** 969-997, 1936	..	..	B	I. C. (near P. C.)	Photograph of circle of Willis
27	Taylor, A. B., and Whitfield, A. G. W.: Quart. J. Med. **29:** 461-472, 1936	..	..	..	M. C.	Rupture of right
28	Thorpe, F. T., and Clegg, J. L.: J. Path. & Bact. **42:** 657-664, 1936	64	F	A	I. C. (intracranial)	Also aneurysm right postcerebral and one of branch of P. Com.
29	Frazier, C. H.: Surg., Gynec. & Obst. **62:** 1-33, 1936	53	M	A	I. C. (intracranial)	Rupture of left
30	Dial and Maurer [47]	49	F (C)	S (?)	I. C. (at P. Com.)	Although syphilis present, syphilitic nature of aneurysms doubtful
31	Bozzoli, A.: Riv. oto-neuro-oftal. **44:** 304-306, 1937	59	M	A	I. C. (carotid canal)	Seen by x-rays; pressure on pituitary

TABLE 4.—*Symmetrical Bilateral Intracranial Aneurysms*—Continued

Case No.	Author and Reference	Age	Sex	Probable Type *	Site	Comments
32	Jefferson, G.: Brit. J. Surg. **26:** 267-302, 1938	72	F	A	I. C. (carotid canal)	.....
33	Hamby, W. B.: J. Internat. Coll. Surgeons **3:** 216-222, 1942	68	F	A	I. C. (intracranial)	Photograph of aneurysms
34	Walsh, F. B., and King, A. B.: Arch. Ophth. **27:** 1-33, 1942	72	M	..	A. C. (at A. Com.)	Positive blood and spinal fluid Wassermann test
35	Walsh and King	70	F	B	M. C.	Rupture of right, also aneurysm on basilar and 4th aneurysm on A. Com.; Case 45 (Dandy)
36	Walsh and King	50	M (C)	A	I. C. (intracranial)	Hemorrhage from A-V aneurysm, left occipital lobe; Case 41 (Dandy)
37	Mitchell and Angrist [45]	45	M	B	A. C.	Rupture of both aneurysms
38	Dandy,[1] Table B-III	67	M	A	I. C. (intracranial)	.....
39	Dandy,[1] Table B-V	64	F	A	I. C., V. (intracranial)	Also S-shaped basilar aneurysm; drawing (Fig. 9, p. 36) typical of fusiform types
40	Dandy,[1] Table B-VI	52	M	A	I. C. (intracranial)	.....
41	Dandy,[1] Table B-XIX	50	M (C)	B	I. C. (intracranial)	Death from rupture of left occipital A-V aneurysm; Case 36 (Walsh and King)
42	Dandy,[1] Table B-XXII	35	F (C)	B	I. C. (intracranial)	Rupture of right; similar, pea-sized aneurysm on left, slightly asymmetric
43	Dandy,[1] Table B-XXXI	33	M	B	I. C. (intracranial)	Rupture of left; Case 17 (Albright) and Case 18 (Forbus)
44	Dandy,[1] Table B-XXXVI	52	M (C)	B	I. C. (intracranial)	Rupture of 3d aneurysm on A. Com.
45	Dandy,[1] Table D-XIX	70	F	B	M. C. (1st branch)	Aneurysm also on basilar and another on A. Com.; Case 35 (Walsh & King)
46	Dandy,[1] Table D-XXI	43	F	B	M. C. (at A. C.)	.....
47	Suter, W.: Schweiz. med. Wchnschr. **79:** 471-476, 1949	55	M	B	I. C.	Ruptured aneurysm A. Com.; anomaly circle of Willis
48	Robertson, E. G.: Brain **72:** 150-185, 1949	47	M	B	I. C.	Rupture of left
49	Falconer, M. A.: Brit. M. J. **1:** 809-813, 1950	38	M	B	I. C. (intracranial)	Found by angiography
50	Hyland, H. H.: Arch. Neurol. & Psychiat. **63:** 61-78, 1950 (Case 1)	51	M	A	M. C.	Rupture of left; photograph showing virtual symmetry; 3d aneurysm, basilar
51	Poppen, J. L.: J. Neurosurg. **8:** 75-102, 1951 (Case 1)	66	F	..	I. C.	Rupture of left, later rupture of right; anomalous circle of Willis
52	Bassett, R. C.; List, C. F., and Lemmen, L. J.: Surg., Gynec. & Obst. **95:** 701-708, 1952	..	..	..	I. C. (intracranial)	Located by angiography
53	Norlén, G.: Proc. Roy. Soc. Med. **45:** 291-298, 1952	39	F	B	I. C. (intracranial)	Found by angiography
54	Browne, E. F., and Meyer, J. S.: New England J. Med. **247:** 671-672, 1952	38	M (C)	B	I. C. (intracranial)	Rupture of 3d aneurysm, A. Com.; also pheochromocytoma; B. P. 160/90
55	Bigelow (Albany Hospital)	64	M	B	I. C. (intracranial)	Rupture of right; incipient aneurysm A. Com.
56	Bigelow	63	M	A	I. C. (intracranial)	.....
57	Bigelow	38	F	B	M. C. (1st branch)	Rupture of left; also unruptured aneurysm 2d branch L. M. C.
58	Bigelow	56	M	A	I. C. (at P. Com.)	Rupture of right
59	Bigelow	47	F	B	A. C.	Found at operation; pressure on optic nerves
60	Bigelow	67	F	A	I. C. (intracranial)	Found at operation
61	Bigelow	49	F	A	V.	Found at operation
62	Bigelow	74	F	A	I. C. (intracranial)	Incidental finding at autopsy

* A, arteriosclerotic; B, berry, or congenital; T, traumatic; S, syphilitic.

of one intracranial aneurysm makes the presence of two or more other intracranial aneurysms a distinct possibility.

Since intracranial aneurysms may often be multiple, the next step is to consider their relationship, if any, to aneurysms elsewhere, in other words, the presence of extracranial aneurysms in patients with intracranial aneurysms. Does the presence of the one either predispose to or increase the probability of the other? #

The number of instances in which both intracranial and extracranial aneurysms have been present are so infrequent as to make such an association appear fortuitous. Nevin and Williams (Table 3, Case 69) reported the case of a 45-year-old woman who bled to death from a ruptured splenic artery. Four intracranial aneurysms were present. Eppinger (Table 3, Case 17) also recorded the presence of nine intracranial aneurysms in a 23-year-old man who had a ruptured aneurysm of the left arteria femoris profunda. On a few occasions intracerebral miliary aneurysms have been reported in association with miliary aneurysms elsewhere in the body. Instances of aortic and intracerebral aneurysms are recorded,* but without multiple intracranial lesions.

No coexistence of intracranial aneurysms, whether single or multiple, with multiple aneurysms of other arteries, such as the coronary, splenic, or renal arteries, has been observed. Only in the case of mycotic aneurysms is it common for arterial aneurysms to be present at several sites. Presumably syphilitic aneurysms could also be widely distributed, but acceptable verified instances are lacking.

One might wonder whether various types of intracranial vascular abnormalities, such as telangiectasia or arteriovenous fistula or angioma, occur frequently in association with aneurysms. Dandy, as well as Walsh and King,† have reported independently the presence of bilateral symmetrical carotid artery aneurysm in a 50-year-old Negro man who died of the effects of hemorrhage from an arteriovenous aneurysm of the left occipital lobe. Aring ‡ reported the presence of what he called a massive intracranial cavernous angioma, presumably a racemose arteriovenous aneurysm, in association with three intracranial aneurysms in a 30-year-old woman. These few citations serve but to emphasize the lack of correlation between most types of intracranial vascular lesions and intracranial aneurysms.

There are, moreover, three lesions which have been found in association with intracranial aneurysms sufficiently often to be noteworthy: (1) anomalies of the circle of Willis, (2) coarctation of the aorta, and (3) congenital polycystic renal disease. The berry, or so-called congenital intracranial aneurysm, is the type found most frequently in association with these conditions. Since all of these lesions represent embryonic or developmental defects, the coexistence of intracranial aneurysms with these three disorders may represent a relationship that is more than merely coincidental. As Forster and Alpers [20] have pointed out, "Congenital anomalies are notoriously prone to occur in combinations, so that it is not surprising that congenital aneurysms have been reported in association with other developmental defects." Therefore, the fairly frequent association of these lesions with multiple intracranial aneurysms merits attention.

Anomalies of the Circle of Willis.—Several studies have shown that anomalies of the circle of Willis, by which is meant variations of the normal structure of the circle, may be found to occur in approximately 50% of

As an interesting historical footnote, reference is made to an opinion expressed by Morgagni [4] (Bk. I, Letter III, Case 8) nearly two centuries ago. His friend, the physician Bernardino Ramazzini, a few years prior to his death from apoplexy, in 1714, had developed symmetrical aneurysms on the dorsum of each hand in the angle between the thumb and the forefinger. Morgagni suggested that an intracranial aneurysm might have been present and that its rupture could have been responsible for Ramazzini's death. The true cause of the apoplexy, however, was not determined, since an autopsy was not performed.

* References 18 and 19.

† Table 4, Cases 36 and 41.

‡ Table 3, Case 97.

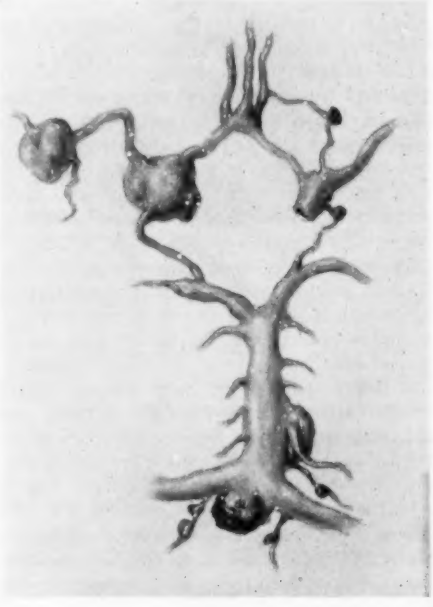
Fig. 2.—Circle of Willis, in which nine aneurysms may be seen. A large aneurysm of the left middle cerebral artery had been removed for histologic study. Evidence of rupture of the basilar aneurysm at the vertebral bifurcation is recognizable. The anomalous third, or middle, anterior cerebral artery, as well as the aneurysm on an accessory vessel between the right anterior and middle cerebral arteries, may be seen.

brains which are carefully examined for such changes. Frequently, when intracranial aneurysms, especially those of the berry, or congenital, type are found, there is also a congenital malformation in the arterial circuit at the base of the brain. Blackburn, incidentally, noted 3 cases of intracranial aneurysms, 1 of which was multiple,§ among 43 tabulated cases of anomalies of the circle of Willis. As noted in Table 3, such anomalies may also be present with multiple, as well as with single, aneurysms.‖

In 19 of 56 cases in which congenital, or berry, intracranial aneurysms were found at autopsy in the Albany Hospital, anomalies of the circle of Willis were also present. An abnormality of the circle of Willis was also found in six cases in which no intracranial aneurysm was found. It thus appeared that nearly 34% of congenital aneurysms were associated with recognizable morphologic abnormalities in the arterial circuit at the base. Four of the 19 cases had multiple aneurysms, with rupture or bleeding from one of them. Although the nature of the anomalies of the circle of Willis varied greatly in the different cases, in two instances of multiple aneurysm, as well as in one instance of a single aneurysm, there was a third, or middle, anterior cerebral artery arising from the anterior communicating branch (Figs. 2 and 3). Abnormalities of the posterior communicating and posterior cerebral arteries, especially with regard to number or symmetry of size or location, were the most frequent anomalies noted, and, in fact, some such abnormality of these vessels was present in the three other instances in which multiple aneurysms were present with these vascular developmental aberrations.

Possibly the developmental abnormalities of the circle of Willis may be correlated with congenital developmental defects which involve the walls or portions of the walls of the arteries, thereby leading to their weakness and predisposing to aneurysm formation. Furthermore, the altered hemodynam-

Fig. 3.—Pictorial reconstruction of circle of Willis shown in Figure 2, emphasizing aneurysms and showing approximate size and location of middle cerebral aneurysm.



§ Table 3, Case 21.

‖ Table 3, Cases 2, 21; Table 4, Cases 15, 22, 47, 51.

ics in the vascular tree resulting from these vascular anomalies may favor the development of aneurysms. Since several intracranial aneurysms occurred in one instance in which several anomalies of the circle of Willis were present, this case is presented herewith.

CASE 1.—C. D., a 52-year-old white woman, was brought to the hospital in coma. She had been entirely well until one week prior to admission, when she developed sudden stiffness and pain in the neck. Because of persistence of these symptoms, she consulted a physician three days later, who could find no neurologic abnormalities. On the evening of admission she suddenly became comatose, and, although immediately transferred to the hospital, she died within two minutes of her arrival.

An autopsy, performed 11 hours after death, disclosed all significant pathologic abnormalities to be within the cranial cavity. The brain was of normal size and contour and weighed 1,180 gm. Diffuse subarachnoid hemorrhage, which was prominent over the base, did not extend over the convex surfaces of the cerebral hemispheres. It was immediately apparent that rupture of a fairly large intracranial aneurysm which originated from the left vertebral artery was the source of the bleeding. After block removal of the arteries at the base of the brain, a total of 10 aneurysms were found.

The ruptured aneurysm measured 1.5 cm. in diameter and was situated at the junction of the vertebral arteries with the basilar. It was the only one responsible for the hemorrhage, since none of the other aneurysms had ruptured. Three of the other aneurysms were also large, measuring from 1.0 to 1.5 cm. in diameter. One of these originated at the junction of the basilar and the right anterior inferior cerebellar artery; another, at the bifurcation of the left middle cerebral artery, and the third, at the junction of the left internal carotid with the middle cerebral artery. This last aneurysm was so large, and involved so much of the internal carotid artery, that the carotid termination of the posterior communicating branch was incorporated within the aneurysmal dilatation.

The remaining six aneurysms were smaller, saccular outpouchings not near arterial bifurcations. They measured less than 0.5 cm. in greatest dimension and were located as follows: two on the left anterior spinal artery, one on the right anterior spinal artery, one on the right anterior inferior cerebellar artery, one on the right posterior communicating artery (this branch was considerably smaller than the corresponding left branch), and one on an accessory artery joining the right anterior cerebral and the right middle cerebral artery.

Three distinct anomalies of development of the circle of Willis were also noted. The first consisted of an anomalous third (or middle) anterior cerebral artery originating from the anterior communicating artery and extending forward. The second consisted of a supernumerary artery which extended from the right anterior cerebral artery to the right middle cerebral artery. The third anomaly was a right posterior communicating artery of such small caliber that it was one-third the diameter of its mate on the left (Figs. 2, 3).

Coarctation of the Aorta.—Although there are only a few recorded cases in which coarctation of the aorta has been associated with intracranial aneurysms, the association of coarctation of the aorta with various vascular anomalies is well known and generally accepted as a manifestation of simultaneously occurring developmental defects. The extreme degree of carotid artery hypertension that so often characterizes coarctation presumably predisposes to the rupture of intracranial aneurysms when they are present, and may even contribute to their development as well. Intracranial aneurysms were present in 16 of 304 cases of coarctation of the aorta with autopsy collected from the literature by Wright.[21] At least two other cases have been reported, one by Edwards, Christiansen, and Clagett ¶ and the other by Bigelow,[22] which, together with the case below, make a total of 19 cases, in 8 of which multiple intracranial aneurysms were present,# or approximately 40%. Consequently, whenever intracranial aneurysms have been found in association with aortic coarctation, a high percentage of them have been multiple. Recently such a case came to autopsy at the Albany Hospital. A brief summary is presented herewith.

CASE 2.—J. M., A 50-year-old white man, entered the hospital because of severe headache and vomiting, which had developed suddenly on the day previous. He was known to have had hypertension for 27 years, and coarctation of the aorta had been discovered 14 years previously. At the time, it was thought that he had suffered a subarachnoid hemorrhage, and a lumbar tap revealed the presence of 1,430,000 erythrocytes per cubic millimeter. He died on the third hospital day.

Necropsy confirmed the presence of a diffuse subarachnoid hemorrhage but disclosed also a massive hemorrhage of the right frontal lobe. The

¶ Table 3, Case 99.

Table 3, Cases 39 (43), 45, 47, 75, 85, 87, 99 and 133.

source of these hemorrhages proved to be a ruptured berry aneurysm located on the posterior aspect of the anterior communicating artery. A second, smaller and unruptured, berry aneurysm, measuring 0.3 by 0.3 by 0.2 cm. in size, was located immediately adjacent to the larger aneurysm (Fig. 4), and an anomalous third anterior cerebral artery arose from the anterior communicating artery and pursued a middle course anteriorly to the corpus callosum.

The aorta distal to the ligamentum arteriosum was markedly constricted to about 0.2 cm. for a distance of about 0.5 cm., a typical coarctation of adult type. Proximal to this zone of narrowing the aorta was sclerosed. Distal to it the vessel was also

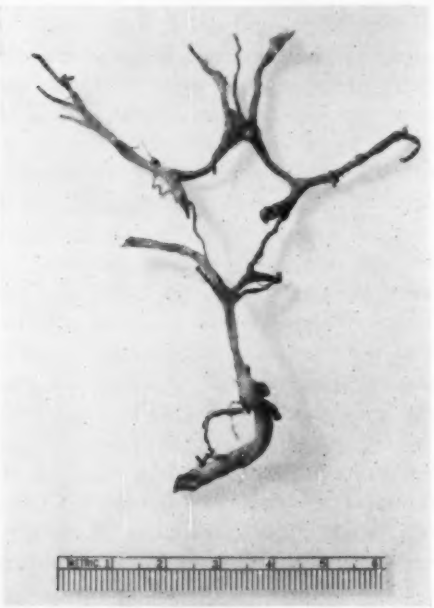


Fig. 4.—Circle of Willis showing two aneurysms on the anterior communicating artery, with rupture of one of them. An anomalous third, or middle, anterior cerebral artery is present.

sclerosed but was of normal diameter. The first two intercostal arteries beyond the constriction were remarkable in that each had a large fusiform aneurysm where they originated from the aorta.

The heart weighed 550 gm. The right and medial cusps of the aortic valve were fused, so that only two cusps were present.

Nearly all intracranial aneurysms, whether single or multiple, in association with coarctation have been present on the carotid circuit, where the effects of hypertension are most marked. As a result most instances of rupture have also involved the carotid, and not the vertebral or basilar, tree. One exception to this general rule was noted by Walker and Livingston (Table 3, Case 75). In their case a 17-year-old youth with coarctation of the aorta died as a result of subarachnoid hemorrhage, which was thought to be due to the rupture of one of several aneurysms of the left vertebral artery.

Congenital Polycystic Renal Disease.—So many cases of coexistent intracranial aneurysms and renal polycystic disease have been noted that Bigelow [22] has suggested that this latter disorder may represent but one manifestation of a group of disseminated embryonic defects, somewhat analogous to tuberous sclerosis, neurofibromatosis of von Recklinghausen, or Lindau-von Hippel disease. In his study some 32 acceptable cases were collected from the literature, to which he added 3 others. Since that report appeared, some 9 other cases have been located, giving a total of 44 cases of this curious association. Three cases were reported both by Hamby [2] and by Poutasse, Gardner, and McCormack.[23] Sahs * added two cases to the two cases he had previously reported with Keil,[24] and a single case was mentioned in passing by Steelman and others.[25] Among the 44 cases there were 7 instances of multiple intracranial aneurysms,† nearly 16%.

In Tables 3 and 4, instances of other unusual lesions, such as pheochromocytoma,‡ in association with multiple intracranial aneurysms are listed under "Comments." None of these lesions occurs frequently enough to suggest other than a chance relationship, although the hypertension associated with a pheochromocytoma, and the development of an intracranial aneurysm might be significant.

ETIOLOGY AND PATHOGENESIS OF MULTIPLE ANEURYSMS

The etiology of intracranial aneurysms has been the subject of many reports and re-

* Table 3, Case 111.

† Table 3, Cases 27, 35, 78, 111, 113, 114, and 129.

‡ Table 4, Case 54.

views; therefore, a detailed historical recapitulation seems superfluous. It is pertinent, however, to comment on the significance of possible causative factors which may be applicable to the etiology of multiple aneurysms. Clearly, mycotic aneurysms, which are dealt with separately, can be set apart as a group, since their etiology and pathogenesis depend primarily on the effects of infectious agents which are extrinsic to the affected artery. Syphilis, which is also considered separately, is of little etiologic significance, and would not be of much importance even if all dubious instances of syphilitic aneurysms were accepted without reservation.

One of the most complex and difficult aspects of the problem of etiology centers on the relative importance of arteriosclerosis, on the one hand, and congenital or developmental defect in the arterial wall, on the other, as the fundamental basis for aneurysm formation. Differences of opinion exist even with regard to the differentiation of arteriosclerotic from berry, or "congenital," aneurysms. Furthermore, even when an aneurysm is conceded to be of the "congenital" type, there are differences of opinion as to the nature of the vascular defect which results in the development of the aneurysm. Even the criteria for distinguishing arteriosclerotic from "congenital" aneurysms are not clear. Thus, it is hardly helpful to designate aneurysms as arteriosclerotic or congenital, or of other etiology for that matter, simply on the basis of opinions given by individual authors, which often cannot be substantiated.

Certainly, fusiform aneurysms, often with thickening and calcification of their walls, are generally due primarily to arteriosclerosis. They are similar to fusiform arteriosclerotic aneurysms as they occur in other arteries, particularly the aorta and the common iliac, common carotid, and cervical portion of the internal carotid arteries. Furthermore, those aneurysms which involve the entire circumference of the artery, forming an ovoid or large spherical swelling, are usually only variations in form of the fusiform aneurysm. Yet there is the possibility that some fusiform aneurysms are not of arteriosclerotic origin, especially when they occur in younger persons. Alpers and Ryan,[26] for instance, report a fusiform aneurysm of the internal carotid artery in a 19-year-old woman. We doubt whether this was of arteriosclerotic origin.

A more significant difficulty arises, however, when an attempt is made to assess the importance of arteriosclerosis in the development of so-called congenital, or "berry," aneurysms. These aneurysms, which develop as a sac or pouch from but a portion, and sometimes only a small portion, of the arterial wall, are generally conceded to be due to some developmental defect, the specific nature of which is unsettled, in the arterial wall itself. Since the presence of intracranial aneurysms in infants under one year of age is such a rare occurrence as to be a medical curiosity, it is doubtful whether the aneurysmal sac is often present in early life. However, the arterial wall defect which is responsible for the later development of the aneurysm may well be present at the time of birth. The zone of weakness, often located at or near the place where an artery bifurcates or gives off a branch, dilates or gives way as a result of several factors. There may be, as has been suggested, several types of anatomic defects, including defects in the elastic lamina or some deficiency of the muscular wall, no one special type of defect necessarily being present in any one case. In addition, there are the unique stresses and strains imposed upon intracerebral vessels which are aggravated if some abnormality of the circle of Willis is present. Alterations, particularly an elevation, in intravascular pressure may also be important. Finally, arteriosclerosis, primarily responsible for the development of true arteriosclerotic aneurysms, must be conceded a possible role in the development of some of these berry aneurysms as well. Often atherosclerosis first appears at sites of arterial branching or bifurcation. Especially is this true in the aorta, where the orifices of the branches are not infrequently the sites of the earliest atherosclerotic lesions. So also the first evidence

of atherosclerosis often appears at these sites in intracranial arteries.

That a complex interrelationship of factors exists in the development of aneurysms can be illustrated still further. Occasionally among multiple aneurysms instances of fusiform or arteriosclerotic type are found in association with those of typical berry type (Fig. 5).

Similarly, multiple intracranial aneurysms of varying type could coexist. As mentioned elsewhere, an aneurysm of the larger intracranial arteries may be associated with intra-

Fig. 5.—Two types of aneurysms encountered in one case. The typical berry aneurysm, which had ruptured, originated in the anterior communicating artery, while the fusiform aneurysm arose from the right vertebral artery.

cerebral miliary aneurysms. While the occurrence of aneurysms of different etiologic types seems theoretically possible, such as mycotic and berry, mycotic and arteriosclerotic, syphilitic and berry, etc., no reports of such combinations have been found. However, a few instances of intracranial arteriovenous aneurysms in association with intracranial aneurysms of berry or fusiform type are on record.§

§ Table 3, Case 97; Table 4, Cases 36 and [illegible].

MILIARY ANEURYSMS

Minute aneurysms, which are so small that they may actually not be recognized on casual examination, occasionally occur on the major intracranial arterial trunks. More frequently, however, they are observed in the thread-like arterioles of the superficial cerebral cortex or the deeper cerebral tissues. Their size in the past was often likened to that of a withered grain of wheat, mustard, or millet seed, and the term soon became "miliary." Aneurysms of this category generally measure less than 1.0 mm. in diameter and have appeared as spindle-shaped, globular, or hourglass dilatations of the small intracranial arteries. When present at all, they have usually been found in considerable numbers, rather than as single, isolated lesions. Cruveilhier, in his atlas published in 1835, illustrated multiple minute hemorrhages as a form of rare capillary apoplexy due to ampullary ectasias, involving all coats of the blood vessels. In 1849, in a short monograph, Pestalozzi [27] noted effusions of blood beneath the raised adventitia of the smaller cerebral arteries and used the term aneurysma spuria to describe them. In a general discussion of aneurysms, Virchow,[28] in 1851, stated that he had often seen minute vascular lesions, which he called dissecting aneurysms, in apoplectic brains. He also described spindle-shaped dilatations, involving the whole vessel, and a less common sac-like enlargement, due to weakening of one side only. In 1859 Gull [29] found a ruptured miliary aneurysm within a focus of intracerebral hemorrhage.

Charcot and Bouchard,[30] in 1868, brought intracerebral miliary aneurysms into prominence by their contention that the major cause of apoplexy or intracerebral hemorrhage was rupture of these structures. They reported 60 cases of cerebral apoplexy, in each of which these miliary aneurysms, ranging in number from two to hundreds, were present in the brain. These lesions were said to be visible to the naked eye as small globular or fusiform structures, varying from 0.2 to 1.0 mm. in size on vessels ranging from 0.03 to 0.25 mm. in diameter, located most

frequently within the cortical tissues of the cerebral hemispheres. The aneurysms were considered to be the result of periarteritis, diffuse in type, that apparently originated in the adventitia and extended into the media, and then underwent atrophy or actually disappeared. Similar aneurysms were occasionally noted in other viscera as well.

Following this publication, there was widespread interest in intracerebral miliary aneurysms, and numerous confirmatory communications appeared. Charlewood Turner,[31] however, in 1882 expressed doubt as to their significance. Eppinger,[32] also, denied that these miliary lesions were true aneurysms. He believed them to be a form of dissecting aneurysm (aneurysma dissecans).

Thereafter, reports about intracerebral aneurysms became less numerous. Both Ellis [33] and Pick [34] felt that they were due to arteriosclerosis rather than to inflammation and that they probably were of two types, a fusiform type, which was a dissecting, or spurious, aneurysm, with blood in the adventitia forming the supposed dilatation, and a saccular type, which was a true aneurysm. Pick also pointed out that only the spurious, or dissecting, aneurysm ever ruptured and that the true, or Charcot-Bouchard, aneurysm never did. Since 1910 there have been only occasional isolated reports on this subject,‖ and it is clear that these miliary aneurysms do not represent a significant factor in the development of massive intracerebral hemorrhage.

In a few instances aneurysms of the intracerebral or miliary type have been found in association with the larger aneurysms located on the major intracranial arteries at the base of the brain. Notably, there is the case of Bouchard,[37] one of Bourneville's,¶ and one of Barlow's.# In Bouchard's case, the brain of a 61-year-old woman exhibited an aneurysmal dilatation of the basilar artery, as well as two miliary aneurysms in the left cerebral hemisphere. Bourneville's and Barlow's cases are summarized in Table 3. The significance of this association, if any, is uncertain.

If one peruses the abundant literature on intracerebral miliary aneurysms between 1870 and 1910, one cannot but be curious as to whatever became of these lesions. Over several years at the Albany Hospital our attempts to find such lesions in the brains of patients who have died of, or who have suffered from, intracerebral hemorrhage have been unsuccessful. It seems unlikely that the perivascular accumulation of lymphocytes or blood within the adventitia of intracerebral vessels commonly seen in brain sections from intracerebral hemorrhage can represent the changes described in the older literature.

One might wonder whether these lesions represented but a curious artifact of these vessels, produced by the manner in which the brains were studied. Could the inflammatory lesions of Charcot, seen not only in the intracerebral vessels but in other viscera as well, have been instances of periarteritis nodosa? Could some of these lesions represent the disorder which today is known as hereditary familial telangiectasia? Did these patients suffer from a disease, not recognized then, and now no longer a widespread or serious clinical problem, such as vitamin C deficiency? Or were these lesions manifestations of a then unrecognized blood dyscrasia, such as thrombocytopenia purpura, pernicious anemia, or leukemia?

While these questions may be speculative, there is one point that should be emphasized. The term miliary as used in the older literature referred literally to minute vascular protuberances which were generally located intracerebrally or on the convex surfaces of the hemispheres. Consequently, "miliary" has been so inextricably linked with these minute intracerebral lesions that the use of this term today as a synonym for the berry, or saccular, aneurysm of the major arterial circuit at the base of the brain is somewhat misleading, even when, as occasionally happens, these latter aneurysms are so small as to be truly miliary in size.

‖ Hassin.[35] Green.[36]

¶ Table 3, Case 9.

Table 3, Case 15.

MYCOTIC ANEURYSMS

The term mycotic, first proposed by Osler in 1885,[38] refers to aneurysms which develop as a result of the weakening of arterial walls by bacterial infection. Multiple intracranial aneurysms of this type are not often encountered. Since the formation of such aneurysms is due to factors extrinsic, and not intrinsic, to the artery, these lesions should be considered as a separate group, apart from other aneurysms.

Bacterial infection may invade the vessel from without or within. External involvement usually occurs as a result of extension from an adjacent inflammatory focus, such as a tuberculous cavity or an abscess. This mode of aneurysm formation, though of little importance in relation to intracranial arteries, is sometimes described as a cause. An instance of multiple aneurysms of this type was noted in one of Brown's cases [39] in which there was "a large aneurysm of the basilar artery and another of the left superior cerebellar artery which were associated with a tuberculoma in the left lobe of the cerebellum and were considered to be due to tuberculous involvement of the arterial walls."

The only significant factor in the development of intracranial mycotic aneurysms is the infected embolus, which weakens the arterial wall from within. Most aneurysms of this type result from septic emboli, particularly in cases of bacterial endocarditis. It is the general consensus that the plugging of arterial lumens by septic emboli is the manner in which the majority of mycotic aneurysms develop. It is also noteworthy that the majority of mycotic aneurysms occur in small, often minute, arterial twigs, generally small cerebral or meningeal arteries.

In reviewing the 19th century literature on aneurysms, it is often impossible to decide whether or not any of the aneurysms was actually of mycotic origin. For example, the only information available may be that an intracranial aneurysm was present in a patient who also had vegetative endocarditis. In such cases, without further corroboration, it is as reasonable to assume that the two processes were unrelated as to assume the opposite. To indicate the difficulties encountered, consider the case of the 18-year-old youth described by Pitt [40] who was found at autopsy to have symmetrical bilateral aneurysm of both middle cerebral arteries with rupture of the lesion on the right. Pitt concluded that the symmetry of the aneurysms and the youth of the patient indicated the embolic etiology of the aneurysms, although there was no mention of endocarditis or other possible sources of septic emboli. Truly, a nonembolic etiology seems more plausible, for, granted that emboli can lodge at random throughout the intracranial vascular tree, it would be most unusual for bilateral symmetrical embolization of two intracerebral arteries to result in the development of two similarly sized aneurysms. Such a coincidence from a chance deposition of infective emboli would be truly extraordinary. Most certainly the finding would not of itself be indicative of an embolic etiology.

Only a small number of cases of mycotic cerebral aneurysms have been reported. McDonald and Korb's [3] tabulation of 1,125 cases of intracranial aneurysms lists only 78 as mycotic or embolic. Of these, 45 were on some branch of the middle cerebral artery. Thus, over one-half such aneurysms have occurred in the middle cerebral artery circuit. Beadles [41] stated that a high proportion of mycotic aneurysms also occurred in the posterior cerebral arteries. Possibly the midlde and posterior cerebral arteries are more readily subject to mycotic aneurysmal formation than are other arteries, since these vessels represent the most direct route for septic emboli to take after reaching the intracranial circuit. Certainly, the flow to the middle cerebral and posterior cerebral arteries from the internal carotid and basilar arteries, respectively, requires less angulation or sharp change of direction than flow into the other intracranial arteries requires. In recent years, because of the advent of antibiotic therapy, intracranial mycotic aneurysms have become relatively uncommon and of less importance. While all reports in the older literature of mycotic aneurysms represents postmortem studies, surgical therapy is pos-

sible. Campbell and Burklund [42] have reported successful removal of a mycotic aneurysm from a branch of the middle cerebral artery.

Numerous instances of intracranial mycotic aneurysms associated with similar lesions elsewhere in the arterial circuit have been recorded. Obviously, septic emboli may produce aneurysms almost anywhere in the body, and it is but fortuitous if one or more of a number of such aneurysms happens to be intracranial. To be sure, death may supervene before many aneurysms appear, but in a few instances an intracranial hemorrhage due to the rupture of a mycotic aneurysm seems to have been the factor immediate responsible for a patient's death, often with signs and symptoms indistinguishable from those which may result from rupture of other types of aneurysms.

Tables 5, 6, and 7 give percentages for multiple mycotic aneurysms whenever reported when a series of mycotic aneurysms are cited. Whether these aneurysms are single or multiple, there is a decided predilection for the middle cerebral arteries, with small subcortical or arachnoidal arterioles often involved, the probability of involvement of one of the middle cerebral arteries or its branches being better than 50%.

TABLE 5.—*Incidence of Multiple Intracranial Mycotic Aneurysms*

Case No.	Author and Reference	Aneurysms	No. Cases	Multiple Cases	Mycotic Type, Per Cent
1	Ponfick: Virchows Arch. path. Anat. **58:** 528-571, 1873	6	5	1	20
2	Simmonds, M.: Deutsche med. Wchnschr. **27:** 353-356, 1901	10	7	1	14
3	Fearnsides, E. G.: Brain **39:** 224-296, 1916	15	13	2	15
4	Drennan, A. M.: New Zealand M. J. **20:** 324-349, 1921	3	2	1	50
5	Green, F. H. K.: Quart. J. Med. **21:** 419-432, 1928	6	5	1	20
6	Mitchell and Angrist [45]	Many	10	3	30
7	Dandy [1]	6	5	1	20
8	Bigelow	Many	2	1	50
	Total.....		49	11	22

SYPHILITIC ANEURYSMS

Since syphilis is responsible for a number of arterial aneurysms that may occur throughout the body, especially in the thoracic aorta, it might be surmised that this infection would be of significance in the development of intracranial aneurysms. In the older literature the presence of syphilis in patients with intracranial aneurysms was considered sufficient evidence for a cause and effect relationship, even when the diagnosis of syphilis appears to have been based on dubious clinical grounds. Little consideration seems to have been given to the fact that, even when syphilis was unquestionably present in a patient with intracranial aneurysms, the disease in many cases was undoubtedly merely coincidental.

Martland [43] has pointed out that syphilis as it involves the cerebral arteries manifests itself as periarteritis and/or proliferative endarteritis, in which occlusion or thrombus formation may occur. The development of an aneurysm under such conditions, in which the arterial wall is thickened and the lumen virtually obliterated, is highly unlikely except in the larger intracranial arteries, such as the carotids. Nevertheless, the inflamed and weakened arterial walls on occasion may undergo aneurysmal dilatation. The pathologic lesions described and illustrated by Maass [44] can be accepted as bona fide. The two instances of intracranial aneurysms considered syphilitic by Mitchell and Angrist [45] likewise seem acceptable.

In review of the cases of intracranial aneurysms at the Albany Hospital, two of the patients were reported as syphilitic. In the first, a ruptured aneurysm was considered syphilitic because the patient, a 61-year-old man, had syphilis. Since no evidence of arteritis suggestive of syphilis was present in any of the cerebral arteries, this aneurysm

has now been reclassified and is no longer considered to be of syphilitic origin. The second aneurysm which was considered to be of syphilitic origin occurred in an artery that showed marked periarteritis and proliferative endarteritis. Consequently the aneurysm is still considered to be syphilitic in origin. While other acceptable instances of syphilitic intracranial aneurysms may have been reported, they are infrequent, and certainly today syphilis can be considered a relatively insignificant etiologic factor.

It is not surprising, therefore, that acceptable, or even probable, instances of multiple syphilitic intracranial aneurysms have been extremely rare. Maass,[44] in a series of eight cases of syphilitic intracranial aneurysms, reported the presence of two syphilitic aneurysms in a 69-year-old woman. The cerebral vessels were atherosclerotic, and a ruptured pin-head-sized aneurysm was present on the right middle cerebral artery, while an unruptured aneurysm was found on the anterior communicating artery. Thus, nine

TABLE 6.—*Individual Cases of Multiple Intracranial Mycotic Aneurysms*

Case No.	Author and Reference	Age	Sex	Site	Comment
1	Ponfick: Virchows Arch. path. Anat. **58:** 528-571, 1873	27	M	R. M. C.; L. arachnoid over occiput	Verrucous endocarditis; aneurysms of splenic and renal arteries
2	Eppinger [32]	49	F	Both M. C., and L. P. C.	Several aneurysms in cortical branches
3	Eppinger	30	M	R. V.,* 2 R. V.	.....
4	Pitt [40]	18	M	L. M. C., R. M. C.	Mycotic nature doubtful (See Table 4, Case 7)
5	Simmonds, M.: Deutsche med. Wchnschr. **27:** 353-356, 1901	27	F	Ba, 3 R. M. C.	Recurrent endocarditis
6	Fearnsides, E. G.: Brain **39:** 224-296, 1916	..	M	Branch L. M. C.,* branch L. M. C., L. Femoris profunda *	Streptococcal endocarditis
7	Fearnsides	..	F	Branch L. M. C.,* branch R. A. C.*	Puerperal septicemia
8	Drennan, A. M.: New Zealand M. J. **20:** 324-349, 1921	44	M	R. M. C., branch L. A. C.*	Ulcerative endocarditis; history of syphilis
9	Taylor, A. B., and Whitfield, A. G. W.: Quart. J. Med. **5:** 461-472, 1936	59	F	2 of circle of Willis	.....
10	Mitchell and Angrist [45]	51	M	Multiple subcortical	Staphylococcus aureus sepsis
11	Mitchell and Angrist [45]	17	F	Multiple subcortical	Staphylococcus aureus sepsis
12	Mitchell and Angrist [45]	11	F	Two, convexity of parietal and occipital lobes	Subacute bacterial endocarditis
13	Dandy [1]	13	F	R. M. C.,* P. C.*	Bacterial endocarditis
14	Hamby [2]	..	..	R. M. C., Ba	.....
15	Bigelow	40	M	Multiple leptomeningeal *	Pneumonia with bacteremia

* Site of bleeding or rupture.

TABLE 7.—*Mycotic Intracranial Aneurysms in Association with Aneurysms Elsewhere*

Case No.	Author and Reference	Age	Sex	Site	Comment
1	Ponfick: Virchows Arch. path. Anat. **58:** 528-571, 1873	24	M	Small arachnoid * splenic	.....
2	Fearnsides, E. G.: Brain **39:** 224-296, 1916	15	F	L. I. C., celiac,* L. renal	Endocarditis
3	Fearnsides	36	M	L. M. C.,* sup. mesenteric	Endocarditis
4	Parker, H. L.: Arch. Neurol. & Psychiat. **16:** 728-746, 1926	20	M	L. M. C.,* sup. pancreaticoduodenal	Vegetative endocarditis
5	Cleland, J. B.: M. J. Australia **2:** 141-142, 1937	19	F	M. C., abdominal aorta	Malignant endocarditis
6	Herman, G. V.: Am. J. Dis. Child. **53:** 517-524, 1937	8	M	L. M. C., L. post. tibial	Vegetative endocarditis (Strep. viridans)

* Site of bleeding or rupture.

syphilitic aneurysms were present in her eight cases. Carpenter's case [46] was that of a 30-year-old man with aneurysms of both vertebral arteries as they joined the basilar. Since a "gummy" growth was present about the right vertebral artery and many gummata were said to have been attached to the intracerebral arteries, these lesions may have been syphilitic and the aneurysms therefore syphilitic in origin. Dial and Maurer [47] had 13 cases of intracranial aneurysms. The two instances of multiple aneurysms were believed by them to be of syphilitic etiology. To be sure, syphilis was present in both cases. In their Case 10, that of a 49-year-old man, there was inflammation and endarteritis of the intracranial arteries, and the right middle cerebral artery exhibited three small unruptured aneurysms, which may have been syphilitic. In their other case, that of a 49-year-old Negro woman with bilateral symmetrical unruptured aneurysm of both internal carotid arteries, lymphocytes were noted in the media of the artery, but this histological observation is not adequate to establish their syphilitic nature.

SUMMARY

Multiple aneurysms of the arteries of the brain occur in a significantly high percentage of cases of intracranial aneurysms. Analysis and evaluation of these lesions in terms of their multiplicity are presented, especially with respect to their frequency, etiology, pathogenesis, and relationship to other disorders. Tabular reviews of previously reported cases are included.

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ADRENOCORTICAL FUNCTION AND URINARY PHOSPHATE EXCRETION

Comparison in Schizophrenia and in Lysergic Acid Diethylamide-Induced Psychotic Episodes in Normal Persons

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LYSERGIC acid diethylamide (LSD) has come to be regarded with interest in recent years because of its ability to produce hallucinations and other psychotic disturbances when administered to human subjects in exceedingly small doses.* Its activity in amounts of the order of 0.5 γ per kilogram of body weight suggests that it may act as an antimetabolite at a specific site and on a specific enzyme system.

In this paper we wish particularly to consider effects of LSD on aspects of phosphorus metabolism and to compare these data with similar properties in schizophrenic patients.

URINARY INORGANIC PHOSPHATE CHANGES IN RELATION TO ADRENOCORTICAL FUNCTION IN NORMAL MEN AND IN SCHIZOPHRENIC PATIENTS

In a series of studies from the Worcester Foundation carried out in collaboration with the Worcester State Hospital, Pincus, Hoagland, and associates † have reported certain abnormalities in phosphorus metabolism of schizophrenic patients, particularly in relation to the action of adrenocortical hormones. The patients when matched for age with normal controls excrete significantly less inorganic phosphate at rest but show a marked enhancement of phosphate excretion when exposed to stress or when injected with corticotropin or with adrenocortical extract. Table 1 is an analysis of the data and compares inorganic phosphate excretion for three groups of patients and controls in different age ranges for timed urine samples collected from the period of rising until approximately 9:00 a. m. It is to be noted that the data for the oldest group, age 61 to 91 years, comprising 41 normal subjects and 64 patients, are expressed not as milligrams per minute of phosphate excretion but as milligrams per gram of creatinine. The data for this group are part of an extensive Worcester study now in preparation for publication by Dr. Harry Freeman. The patients excrete subnormal amounts of inorganic phosphate in a reduction of the order of 40% to 50%. The basis of selection of the patients and control subjects, all of whom were males, has been described elsewhere.†

Table 2 reviews findings of percent increases in inorganic phosphate excretion for these same patients and controls when subjected to several experimental stresses, to the injection of 25 mg. of corticotropin (Armour LA1A Standard) and to the injection of 10 cc. of Upjohn's Lipo-Adrenal Cortex (adrenal cortex extract; ACE), equivalent to 10 mg. of hydrocortisone. Procedures used in these tests have been described.† In brief, control urine samples were collected from the time of rising until the beginning of the test, at about 9:00 a. m. Each test sample of urine was taken three hours after the beginning of a pursuitmeter stress test, target ball frustration test, or oral glucose tolerance test, or three hours after the injection of corticotropin or adrenocortical extract except in the case of the oldest men, for whom four-

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* References 1 through 5.

† References 6 through 8.

hour samples were used. The tests were all conducted between 9:00 and 11:00 a. m. to avoid variations due to effects of diurnal rhythm on adrenal activity. As Pincus and Hoagland have earlier pointed out,‡ it is clear that the patients, while low excreters of inorganic phosphate, show marked increases in phosphate excretion that are associated with increased levels of adrenocortical hormones brought about by endogenous corticotropin secretion following stress or by injected corticotropin or adrenocortical extract. The reader is referred to earlier papers † for direct measures of adrenal response in the stress tests and following the corticotropin and adrenocortical extract injections. These measures consisted in determinations of total 17-ketosteroids, of corticoids determined as neutral reducing lipids or as formaldehydogenic steroid, and of sodium, potassium, and uric acid. The effect of corticotropin in enhancing phosphate excretion in the patients

TABLE 1.—*Comparison* of Rates of Inorganic Phosphate Excretion of Normal Subjects and of Schizophrenic Patients in Three Age Groups †*

	Age 20-39 Yr.		Age 40-60 Yr.		Age 61-91 Yr.	
	Normals, Mg./Min.	Patients, Mg./Min.	Normals, Mg./Min.	Patients, Mg./Min.	Normals, Mg./Gm. Creatinine	Patients, Mg./Gm. Creatinine
Inorganic phosphate excretion rate.....	0.54	0.26	0.36	0.22	20.8	11.8
Percent comparison of patients and controls in same age groups.....	100	48.2	100	61.1	100	56.7
No. of determinations.....	135 ‡	80 ‡	96 ‡	91 ‡	41 §	64 §

* All comparisons between patients and normal controls are statistically significant at better than the 1% level of confidence.
† References 6 and 8.
‡ An average of approximately three determinations per person.
§ Number of persons, one determination each.

TABLE 2.—*Percent Increases or Decreases* over Pretest Control Values of Excretion of Urinary Inorganic Phosphate in Normal Subjects and in Schizophrenic Patients Following Stresses, Injection of 25 mg. of Corticotropin and Injection of 10 cc. of Adrenocortical Extract (ACE) †*

Nature of Test	Age 20-39 Yr.		Age 40-60 Yr.		Age 61-91 Yr.	
	Controls	Patients	Controls	Patients	Controls	Patients
Pursuitmeter stress	—0.4	+37	—25	+32	....	....
No. of persons.....	15	10	25	17	....	....
Significance (*P*) of difference between normals and patients	....	Not signif.	....	<0.05	....	....
Target ball frustration test.....	— 4	+35	—12	+63	....	....
No. of persons.....	13	11	25	18	....	....
Significance (*P*) of difference between normals and patients	....	Not signif.	....	<0.01	....	....
Oral glucose tolerance test.....	—42	—14	—18	+17	—12	+24
No. of persons.....	14	11	26	31	20	22
Significance (*P*) of difference between normals and patients	....	Not signif.	....	<0.05	....	<0.01
25 mg. corticotropin.....	—21	+127	+ 2	+92	— 3 †	+71 †
No. of persons.....	7	8	26	28	19	28
Significance (*P*) of difference between normals and patients	....	<0.05	....	<0.01	....	<0.01
10 mg. ACE.....	— 7	+109	....	....	....	....
No. of persons.....	9	9	....	....	....	....
Significance (*P*) of difference between normals and patients	....	<0.01	....	....	....	....

* Increases are indicated by +; decreases by —.
† Unless otherwise indicated, urine samples were collected three hours from beginning of the one-hour test or three hours after injection. See References 6 and 8.
‡ Samples collected four hours after injection of corticotropin.

‡ References 6 and 8.

without comparable effect in normal subjects is especially interesting. Thus, in the younger group there is a mean difference of 148% between patients and normal subjects in this regard, the patients showing enhanced excretion. In the middle-aged group this difference is 90%, and in the old group it is 74%. The importance of phosphate bond energy in relation to the body economy makes these observations of special interest.

BEHAVIOR OF INORGANIC PHOSPHATES IN NONPSYCHOTIC SUBJECTS UNDER THE INFLUENCE OF LYSERGIC ACID DIETHYLAMIDE

In the previous Worcester studies, morning pretest samples of urine being used, it was found [8] that schizophrenic patients, in addition to the low rate of excretion of inorganic phosphates, excrete, if anything, slightly increased levels of total 17-ketosteroids, somewhat subnormal amounts of adrenal corticoids, abnormally large amounts of Na, K, and urinary water, and normal amounts of uric acid (Table 1 [8]). Following the standardized stresses that were used, or the administration of 25 mg. of corticotropin, the patients, on the average, show the same percentage increase of corticoids as do the controls, but a significantly smaller percentage increase in output of sodium, potassium, 17-ketosteroids and uric acid.§ These changes contrast sharply with the marked rise in phosphate excretion previously described || and here presented in Table 2. No significant differences in percent changes in eosinophile and lymphocyte counts between groups of patients and controls were found by us at Worcester following these mild stresses or the injection of 25 mg. of corticotropin.

In the present study we have undertaken an experiment on normal subjects designed to compare the foregoing measures of adrenocortical function before the administration of lysergic acid diethylamide (LSD) with those at the peak of its action. Dr. Betty Rubin and Dr. Fred Elmadjian, of the Worcester Foundation, and the technical staffs in their laboratories made the 17-ketosteroid, uric acid, electrolyte, and phosphate determinations.

PROCEDURE

The procedure involved collections of timed urine samples on each of a group of normal male volunteers who came to the Boston Psychopathic Hospital for this study as part of a more extensive investigation of effects of LSD on normal subjects.[3] On the first experimental day a control collection was taken from the time of rising until approximately 9 a. m., and a second control was collected from 9 a. m. to 3 p. m., after which 25 mg. of corticotropin was injected intramuscularly. At approximately 6 p. m. a third urine sample was collected. From the two control samples the subjects' diurnal rhythm of adrenocortical activity is indicated, and the response to corticotropin may be determined from the third sample. The samples were analyzed for rates of excretion of urine, creatinine, 17-ketosteroids, sodium, potassium, inorganic phosphates, and uric acid. In Table 3 this form of experiment is referred to as "1st Control-2d Control-Corticotropin."

On a second experimental day, usually a week or two later, a control collection was made from 7:00 to 9:00 a. m., when the subject was then given LSD by mouth (0.5 to 1.0 γ per kilogram of body weight). The effect of LSD was then measured on the above variables in a urine sample collected from approximately 9:00 a. m. to 3:00 p. m. Immediately after this collection, 25 mg. of corticotropin was injected and the adrenal response to corticotropin during the time of action of LSD was then measured on a 6-o'clock urine sample. This experiment is referred to in Table 4 as "Control-LSD-Corticotropin." Data on 12 normal healthy men (age 20 to 30 years) in 21 experiments have been obtained for analysis. All the subjects experienced psychotic-like experiences for 6 to 10 hours after the administration of LSD.

RESULTS

The data, expressed as means, are summarized in Tables 3 and 4.

Table 3 compares the first control-second-control-corticotropin studies in terms of mean percent changes, as indicated by the column heads. The 17-ketosteroid output is less by 14% in the case of the second control, as might be anticipated from the usual diurnal rhythm.¶ The administration of cor-

|| References 6 and 8.

§ References 6 through 8.

¶ References 10 and 11.

ticotropin increases the 17-ketosteroid output in expected fashion. From diurnal rhythm expectation without corticotropin, this value in the third column would be about 70%, so that there is a rise of approximately 60% following corticotropin. This Table shows that corticotropin causes a retention of sodium. There is evidence of an increased output of both sodium and potassium in the second control over that of the first, and this increase is in contrast with the decreased output of 17-ketosteroids. This finding was unexpected, and we shall comment on it later. The effect of corticotropin on this already rather high potassium output is negligible. Uric acid shows the kind of response to be expected from previous studies.# The second control shows a reduction in diurnal rhythm over the first control, and corticotropin significantly enhances the uric acid output. Phosphates also show a diurnal rhythm, but there is some unexpected increase in output of these phosphates with the administration of corticotropin as compared with the expectancy from Table 2.

There is thus seen the stimulating effect of corticotropin on the adrenal as measured by the 17-ketosteroids, sodium, and uric acid constituents in the control series. The diurnal rhythm pattern, however, is somewhat different from the data we have accumulated in our previous Worcester studies, and the reason for this is probably differences in experimental design. In the investigations by Pincus and associates * of the diurnal variation of adrenocortical action the subjects ate three meals a day. In the Worcester stress studies, on the other hand, including those involving the administration of 25 mg. of corticotropin, the subjects came without breakfast, as they did in the present study. In the former studies they received an injection of 25 mg. of corticotropin at about 9:00 in the morning, and its effect was assayed on samples collected over the next three hours, before lunch. In designing the present experiment, we thought it desirable to have the subjects come without breakfast in order that they might be comparable to the older corticotropin series. We agreed, however,

TABLE 3.—*First Control-Second Control-Corticotropin Experiment*

	Mean Percent Values per Gram Creatinine of Urinary 17-Ketosteroids, Sodium, Potassium, Uric Acid, and Phosphates			
	1st Control	2d Control / 1st Control × 100	Corticotropin / 2d Control × 100	Significance of Difference Between 2d and 3d Columns
17-ks	100	86	128	$P < 0.05$
Na	100	125	83	$P < 0.01$
K	100	147	119	Not significant
Uric acid	100	91	131	$P < 0.05$
Phosphates	100	66	162	$P < 0.02$

TABLE 4.—*Control-LSD-Corticotropin Experiments*

	Mean Percent Values per Gram Creatinine of Urinary 17-Ketosteroids, Sodium, Potassium, Uric Acid, and Phosphates			
	Control	LSD / Control × 100	Corticotropin / LSD × 100	Significance of Difference Between 2d and 3d Columns
17-ks	100	129	113	$P < 0.05$
Na	100	136	89	$P < 0.05$
K	100	113	131	Not significant
Uric acid	100	196	107	Not significant
Phosphates	100	29	289	$P < 0.05$

References 6 through 8.

* References 10 and 11.

to let them have some lunch, and our corticotropin was injected late in the afternoon. We did not believe that this would interfere appreciably with the sequence of events at the time. In the last few months, however, Dr. Elmadjian has found † that the taking of a meal does produce a response of the adrenal cortex. This, then, would tend to elevate signs of adrenal activity in the second control sample and might be expected to give a result somewhat different from the earlier one. We have, for example, not found corticotropin to enhance the output of urinary phosphates in normal men in the short-term, acute experiment involving a morning injection of corticotropin in a fasting subject (Table 2). Clearly, from Table 3, there is such enhancement of urinary phosphate output. Also, the high value of potassium in the second control may limit its percentage rise after corticotropin administration. Potassium is especially affected by the intake of food.

In Table 4 are compared control and LSD samples, and then the effects of corticotropin superimposed upon the action of LSD. To summarize the salient points, LSD in itself apparently stimulates the adrenal, as may be seen from the 17-ketosteroid data. Whereas in Table 3 there is a reduction from 100% to 86% when the first control is compared with the second control, after administration of LSD there is a response of 129% in 17-ketosteroids, in contrast to 86% for the control value of the same period. There is an increased output of sodium following LSD, little change in potassium output, but a marked increase in output of uric acid, indicating the probable release of corticoids. Phosphates, on the other hand, are markedly reduced in output after LSD stimulation, and this we regard as significant, since schizophrenic subjects at rest excrete on the average only about one-half the urinary phosphates produced by normal controls (Table 1). Absolute values of phosphate excretion are here illuminating. Thus, the subjects excrete 0.291 mg. of phosphate per gram of creatinine between 9 a. m. and 3 p. m. on the control day, but only 0.162 mg. per gram of creatinine ($P < 0.05$) for this same period under the influence of LSD. This ratio of 1.8 is similar to that of 2.1 found when populations of normal and schizophrenic men of comparable age are compared by means of the data of Table 1.

When corticotropin stimulation follows LSD, a damping effect on the responsivity to corticotropin is seen in responses of 17-ketosteroids, sodium, and uric acid. Perhaps the most interesting effect, however, is the marked increase in output of urinary phosphate when corticotropin follows LSD. The schizophrenic patient at rest excretes a reduced amount of urinary phosphate (Table 1), but under stress or after injection of adrenocortical extract or corticotropin his output of urinary phosphates is, on the average, greater than that of the normal subjects. Thus, in Table 2, for the younger group, one sees that the output of inorganic phosphate in the schizophrenic patients following 25 mg. of corticotropin increased by 127%, whereas the phosphate output of the controls declined. The urinary phosphate output at rest in schizophrenic subjects is only about one-half that of the normal (Table 1), but corticotropin gives it this large relative increase (Table 2). Thus, Table 4 is interesting in regard to the similarity of behavior of inorganic phosphates in the LSD-treated normal subject as compared with that seen in schizophrenic patients not treated with LSD.

COMMENT

Our findings indicate that LSD appears to stimulate the pituitary-adrenal axis and leaves the adrenal somewhat unresponsive to corticotropin, as measured by changes in excretion of 17-kerosteroids, sodium, and uric acid. The adrenals of schizophrenic patients, as measured by percent changes in these same variables, are also subnormally responsive to corticotropin.‡ The behavior of inorganic phosphate of subjects under the influence of LSD is especially interesting, since it also follows the pattern we at Worcester have

† Unpublished data.

‡ References 6 through 8.

found in schizophrenic patients. These results suggest disturbance of action of a common enzyme system brought about by LSD in normal persons receiving it, or by a related endogenous substance in the case of schizophrenic patients. The findings, however, raise a number of questions. We do not know that the inhibitory effect on the corticotropin response brought about by LSD is specific for this substance. It may be that any injected nonspecific stressing agent would leave the adrenal refractory for a few hours, so that it would be somewhat unresponsive to corticotropin. We have no conclusive answer to this question, although there are two points that militate against the hypothesis. Conn and associates,[12] at the 1953 Laurentian Hormone Conference, reported that the effects of stress and simultaneously administered corticotropin were additive to adrenal response measures. His procedure was different from ours, however, since the stressing agent and the corticotropin were administered at the same time, whereas our corticotropin test had a lag of about six hours after the administration of LSD. The second, and more cogent, point in favor of specificity of action of LSD resides in the peculiar behavior of the urinary phosphates, which so closely resembles the behavior of phosphates in schizophrenic patients both in their repressed excretion by LSD per se and in their enhanced output in response to corticotropin after the administration of LSD.

Evidence of abnormalities of phosphate turnover in schizophrenic patients has been reported by Örström and Squag.[13] These authors measured the radioactive phosphate (P^{32}) turnover of various compounds in blood in chronic schizophrenic patients. Of a number of phosphate fractions analyzed, they reported that the turnover of adenosinetriphosphoric acid (ATP) in the patients showed a considerably lower value than that in controls. They also found that the specific activity of ATP in chronic schizophrenic patients, in a number of phosphate fractions studied, bore little correlation to the specific activity of free phosphorus. These facts indicated to them that in the patients phosphate compounds other than ATP play a role in phosphorus turnover normally involving this substance. In a later paper, Örström[14] reported on a further investigation and presented evidence indicating that phosphoglycolic acid may play a role in phosphate turnover in schizophrenic patients. He found that the low ATP turnover in schizophrenics (0.04 in patients as compared with 0.26 in normal controls) is apparently compensated for by unusual concentration of phosphoglycolic acid in the patients' erythrocytes to the extent of an average of 4 mg. per 100 cc., as compared with 2 mg. per 100 cc. in the erythrocytes of controls. This substance can accept P^{32}, and Örström suggested that it may to some extent compensate for reduced ATP activity in the patients.

Work from the laboratory of Mayer-Gross[15] has indicated that the administration of LSD to 13 schizophrenic patients resulted in a significant accumulation of blood hexosemonophosphate, although psychological symptoms were minimal. However, mescaline given to normal subjects, while producing marked psychological symptoms, was not accompanied by accumulation of hexosemonophosphate. Manometric studies of respiration of guinea pig tissue in this same paper showed that LSD stimulates the respiration of brain tissue. In these brain experiments, hexosemonophosphate accumulated in the vessels in the presence of LSD, which enforced a sparing action on its utilization despite the over-all respiratory increase.

It is of interest to note in passing that Dr. J. R. Bergen, at the Worcester Foundation, has found in unpublished preliminary work that 100 γ of LSD injected into a guinea pig on several occasions reduced its urinary phosphate output from a mean of 47.5 mg. to a mean of 28.8 mg. in 24 hours. The injection of 2.5 mg. of corticotropin in the LSD-treated guinea pig resulted in an increased excretion of phosphate from this level to 60 mg. in 24 hours—an increase of approximately 100%. Similarity of pattern of urinary phosphate excretion in the schizophrenic patients and in the LSD-treated per-

sons is thus seen in the LSD-treated guinea pig. The implication is that adrenocorticoids release phosphate, bound perhaps as excess hexosemonophosphate, in persons under the influence of LSD. A similar mechanism may be involved in the schizophrenic patient through the action of some endogenous unknown chemical agent functioning after the manner of LSD. More work is needed to test this hypothesis.

That adrenal steroids are involved in phosphorylating mechanisms has been demonstrated. Verzar,[16] in a review of work from his laboratory and of the general literature, has shown that adrenalectomy in animals results in a marked reduction of activities of alkaline phosphatase and of phosphorylase in a variety of tissues studied. Phosphoglucomutase activity is also decreased, and these enzyme activities are restored by suitable replacement therapy. The equilibria of several phosphorylating enzyme systems are thus under the influence of adrenocortical hormones, but the steady-state condition of any one substance, such as hexosemonophosphate, in relation to combined effects of LSD and adrenal steroids has not been determined.

Woolley and Shaw [17] have recently suggested the possibility that LSD may operate to inactivate serotonin (5-hydroxytryptamine), known to be plentifully present in the brain,§ and thus bring about abnormalities of behavior. No direct evidence exists for this hypothesis as far as we know, since the role of serotonin in the brain is unknown. Woolley and Shaw point out that LSD and other structurally similar substances known to produce psychotic-like episodes do act as antimetabolites in relation to the action of serotonin on smooth muscle, and they consider that schizophrenia may be a result of serotonin inactivation brought about by the presence of some unknown antimetabolite formed in the patient.

Quastel and his co-workers,[20] in 1933, pointed out that a number of amines, including mescaline, strongly inhibit glucose, lactate, and pyruvate oxidation by brain enzymes. Mann and Quastel,[21] in 1940, showed that a number of amines, including tyramine, indolethylamine (serotonin), and epinephrine, all compete with each other for amine oxidase in brain. They considered that aberrant amine metabolism may be involved in mental disease. Osmond and Smythies,[22] in 1952, pointed out the structural similarity between mescaline and epinephrine and suggested that disturbances of epinephrine metabolism might produce a toxic catechol amine causing psychosis. Hoffer, Osmond, and Smythies [23] reported, on the basis of eight experiments, that adrenochrome, formed in the body from epinephrine or related catechol amines, produced psychotic-like manifestations and suggested that it may be causally related to schizophrenia. However, their particularly impressive experiments were done with an adrenochrome solution which, according to their own report, was "unstable" and "beginning to deteriorate." We, therefore, suggested, in a paper presented at the annual meeting of the American Psychiatric Association in St. Louis, on May 7, 1954,[9] that "adrenoxin," a further degradation product of adrenochrome, might have caused the reported mental symptoms. Heirman,[24] in 1937, was the first to describe the pharmacological action of a substance he called adrenoxin, an oxidation product of adrenochrome, which, in contrast to adrenochrome, is pharmacologically very active and produces effects on the heart and circulation similar to those of LSD, and does so in very small concentrations. Its structure has not been determined, although some of its physical properties have been described by Heirman.[25] It therefore seems to us more likely that adrenoxin, in addition to its physiological effects, may also have the mental effects that Hoffer and associates ascribed, perhaps erroneously, to adrenochrome, and that adrenoxin may well be the active agent in schizophrenia. We were further led to this assumption by the fact that our own experiments with the stable semicarbazone of adrenochrome did not result in the production of mental symptoms, nor have mental symp-

§ References 18 and 19.

toms by the use of this compound been reported in the literature. However, we realize the difference between the molecule of the semicarbazone of adrenochrome and adrenochrome itself. It may well be that the different molecular structure may materially influence the effectiveness of the semicarbazone of adrenochrome as an antimetabolite in competing for position on enzymes or active surfaces of nerve cells if it should penetrate the blood-brain barrier, an event which also has not yet been established. Bacq and associates [26] have shown that adrenochrome semicarbazone is not hydrolyzed in the rabbit, cat, or dog after its administration. The inactivity of the semicarbazone of adrenochrome, however, and the fact that the experiments of Hoffer, Osmond, and Smythies were done with a deteriorating adrenochrome solution, indicate that other derivatives of epinephrine or adrenochrome, especially adrenoxin, should be examined in relation to psychosis-producing properties. We would like to suggest that, from structural considerations, certain epinephrine derivatives, possibly adrenoxin, might be expected to act as antimetabolites to serotonin and, if produced in excess in schizophrenics, might so act.

Genetic factors, clearly demonstrated to play a role in schizophrenia by Kallmann's studies [27] of homozygous and heterozygous twins, imply derangement of enzyme function. The role of possible enzyme derangement as a causal factor in schizophrenia has been discussed by Hoagland.[28] In view of our consideration of phosphorus metabolism, we would suggest that a probable effect of deranged epinephrine metabolism would involve modification of some enzyme or coenzyme system involved in phosphate transfer. Meyerhof and Randall [29] have found that glucose and hexosemonophosphate oxidation in the presence of brain enzymes is markedly inhibited by adrenochrome. The inhibition of the former is 97% and of the latter 96%. Hexosediphosphate oxidation is inhibited 20%. This finding is of special interest in relation to the action of LSD in producing accumulation of hexosemonophosphate, as described by Mayer-Gross in his studies of guinea pig brain.

Several observers || have reported that schizophrenic patients are relatively insensitive to the psychosis-producing action of LSD as compared with normal persons. While various explanations of this are possible, it could be accounted for if we consider that an intrinsic metabolic agent, possibly a derivative of epinephrine, has already acted to block an enzyme receptor, so that added LSD is relatively ineffective in the schizophrenic patients.

Our observations are consistent with the hypothesis that in the schizophrenic patient and in normal persons under the influence of LSD, phosphate tends to become more strongly bound in some organic form than it does in the normal person and that adrenocortical hormones facilitate the release of this binding. It is, of course, possible that the low excretion of inorganic phosphate in the patients could be due to differences in diet and low phosphorus intake, though one would hardly expect so large a dietary phosphate deficiency as would be necessary to account for a basal difference in excretion rate of the order of 50%. Furthermore, if such were the case, one would not expect to encounter the large excretion in the patients following adrenocortical activity. The similarity in phosphate behavior in well-nourished normal subjects under the influence of LSD militates against such an interpretation. Another possibility is that in schizophrenics abnormal kidney function could account for the findings. Many studies, however (see Altschule,[30] for review), have shown kidney function to be normal in these patients. If our endogenous substance in the patients and LSD in normals acted selectively on the kidney to produce similar abnormalities in urinary phosphate excretion, one would expect to find some abnormality in kidney function in the numerous tests carried out on schizophrenic patients.

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It should, of course, be borne in mind that the abnormalities of phosphorus metabolism reported in this paper may not be causal factors in psychotic behavior but may be incidental to more fundamental chemical events responsible for the psychotic manifestations.

SUMMARY

A review of studies from the Worcester Foundation and the Worcester State Hospital of male schizophrenic patients and normal male controls compared in three different age ranges under nonstressful conditions indicates that the patients excrete between 48% and 61% of the urinary inorganic phosphates excreted by the controls.

Following stress or the injection of corticotropin or of adrenocortical extract (Lipo-Adrenal Cortex), these patients show marked increases in output of inorganic phosphate. Such increases are not seen in the control groups.

Normal subjects studied at the Boston Psychopathic Hospital were given LSD sufficient to produce psychotic symptoms. They showed a reduction in the excretion of inorganic urinary phosphate as compared with control values found in the same subjects.

During the period of action of LSD, injection of corticotropin markedly enhances the excretion of urinary inorganic phosphate. Thus, the behavior of phosphates, both at rest and under the impact of adrenocorticoids, in the LSD-treated normal person is similar to that found in schizophrenic patients without LSD.

It is suggested from evidence in the literature and from our data that LSD acts on enzyme systems to facilitate binding of phosphate. A discussion of the role of adrenocorticoids in relation to phosphorylation is presented. It is suggested that adrenocorticoids may release the phosphate from its bound form, accounting for the marked output of urinary phosphate in schizophrenic patients and in normal subjects under the influence of LSD following the action of corticoids.

It is considered that an endogenous derivative of epinephrine metabolism may act in the schizophrenic patients after the manner in which LSD acts in normal persons. This hypothetical antimetabolite appears to mediate its effect, at least in part, via the exchange of phosphate bond energy.

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SUTURING THE SCHIZOPHRENIC SPLIT

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ADVANCE in the therapy of schizophrenia has been handicapped by the lack of a satisfactory understanding, or even a satisfactory working hypothesis, of the nature of the disorder itself. The purpose of this paper is to discuss a working hypothesis and to consider its relation to methods of treatment known to be effective, as well as its possible implications for further or additional methods of treatment. The hypothesis arises in part from a synthesis of ideas borrowed from Hughlings Jackson with ideas borrowed from Eugen Bleuler. It was stimulated particularly by the frustration experiments conducted with rats by Maier [1] and by the results of the Veterans Administration lobotomy research project.*

Human evolution has been in large part a process of adding to the basic animal equipment and behavior higher mental processes centered in recently evolved and highly developed brain structures. In place of depending on the slow adaptation of the species through countless generations, man has evolved an unprecedented adaptiveness in the behavior of the individual. The newer centers have evolved to a high degree the capacity to learn and to control, direct, and inhibit behavior in the interest of long-term satisfactions, at some cost of denying immediate satisfaction to impulses. As is usually the case, the more recently evolved and highly developed structures are the more sensitive, the more easily disturbed. The social drinker depends on this fact to enjoy the freedom of a temporary release from the inhibition of his cortex by partly anesthetizing it with alcohol. The professional anesthetist carries the process a step further, for the relief of the patient and the convenience of the surgeon, by completely knocking out the functioning of the higher centers, while the respiratory center in the medulla continues its normal function.

Evolution toward flexible, adaptable behavior involves evolution away from patterns of behavior rigidly laid down by heredity, such as we see so highly developed among the insects. It involves evolution toward more and more complicated and difficult choices between alternative patterns of behavior. The very existence of such alternative patterns immediately underlines a possibility of conflict, a possibility which is accentuated as choices become more frequent, more complicated, and more evenly balanced. A price we pay for our cerebral hemispheres, for our capacity for foresight, and our capacity to adapt is an accentuated vulnerability to conflict. Lower animals may be caught in conflict, but they do not characteristically live in conflict in the sense that we do.

I should like to venture a physiological characterization of conflict. Physiologically speaking, conflict may be regarded as activation of two (or more) neural patterns tending toward discharges which are mutually incompatible. When two neural patterns tending toward incompatible discharges are activated simultaneously, one may become dominant over the other and may thereby determine the pathway of discharge. On the other hand, each may block the discharge of the other. If the tension in one or both systems is thereby increased, the neural impulses so blocked may be expected to show a tendency to spread into other channels. Such a tendency is clearly demonstrated in one of A. J. Carlson's classical experiments in physiology: If under anesthesia the spinal cord of a dog is hemisected above the segments innervating the phrenic nerve, the diaphragm on the ipsilateral side is immediately

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* References 1 through 5.

paralyzed. If now the contralateral phrenic nerve is transected, thereby checking all nerve impulses to the contralateral diaphragm, diaphragmatic breathing ceases and asphyxia sets in. Carbon dioxide rapidly accumulates in the blood stream and increases the stimulation of the respiratory center in the medulla. Under this stimulation of increased CO_2, the ipsilateral diaphragm begins to move again in breathing, establishing the fact that, with this increased tension of CO_2 in the system, the nerve impulses flowing down the intact side of the spinal cord now cross the midline and activate the intact phrenic nerve.

It may be worth while to review certain broad considerations which relate to these matters. Physiological tensions within animals activate behavior. Behavior serves, with varying degrees of effectiveness, to relieve such tensions. That behavior which is most effective in relieving tensions tends to be repeated. Effective behavior tends almost universally to be patterned behavior, for unpatterned behavior is generally ineffectual. A significant part of human growth is the achievement of more numerous and more highly developed patterns of behavior and of thinking.

We know that patterned behavior is related to patterned neural activity, and it seems reasonable to presume that orderly thinking is also related to definite patterning of neural activity.

A state of acute perplexity and puzzlement, on the other hand, whether in a normal person or in a schizophrenic, seems probably related to a more diffuse and unorganized cerebral activity. The common electroencephalographic findings showing a disappearance of alpha activity and its frequent replacement with low-voltage fast activity suggest this, as does the general subjective state. Thinking no longer proceeds in an orderly fashion along clearly defined pathways but becomes more erratic and even somewhat disorganized, with a subjective mental state of tension and some anxiety. For conflict generates anxiety, which is probably an expression of heightened activity dependent upon a positive feed-back from cortex to diencephalon. The anxiety, in some instances, may evolve even into panic. There is commonly evidence of muscular tensions and autonomic change, as though heightened activity of brain were tending to overflow to somatic and visceral structures.

In a state of conflict, with the activation of two neural patterns tending toward discharges which are mutually incompatible, and which block each other, and particularly with an intensification of activity probably mediated by a positive feed-back of cortex to diencephalon, we might expect the spreading of nerve impulses out of their usual pathways. This spread would represent a relative diffusion of neural excitement, as contrasted with its narrower and more usual channeling. Such diffusion might result in new pathways of discharge, which might effectively relieve the tension in both systems. Such a discharge of tension from two sets of neural pathways would represent a synthesis and may be assumed to be one of the physiological events which accompanies the moment of insight or of creativity.

The person going through conflict which has resulted in puzzlement often evolves a solution. He makes up his mind. He comes to a decision, and he is relieved. Thinking, and, by our hypothesis, neural activity, are suddenly restored from a diffused state to a more patterned character. If this pattern is a new one which harmonizes elements of old patterns in new synthesis and which holds up under reality check, we speak of its appearance as a burst of insight or of creative experience. Tension is reduced and probably the total neural activity commonly drops to a lower level.

It is worth emphasis that the normal person, faced with an intense conflict, may, when he has exhausted his powers of orderly search for a solution, go through a period of anxious, diffuse, and relatively disorganized or fragmented thinking, from which he may emerge with a new synthesis, a new insight.

An acute schizophrenic psychosis commonly begins with an anxious preoccupation with a conflict which leads to a similar dif-

fuseness of thinking. However, the schizophrenic is able neither to resolve his conflict nor to put it aside. The anxious preoccupation leads to schizoid withdrawal. The diffuseness of thinking progresses to a disorganization of thinking or else results in the false solutions of delusion formation, which may sufficiently reduce inner tensions to stabilize the psychosis but which limit the patient's capacity for adaptation.

That which distinguishes the schizophrenic is that his puzzlement does not come to a satisfactory and realistic solution with relief of tension. It persists. The puzzlement, vagueness, relative disconnectedness, and lack of effective organization of thinking which are so common in the early schizophrenic are the psychological accompaniments of brain activity which is diffuse rather than patterned, which is unresolving, and which tends to jam the higher pathways of the brain and reduce their availability for the guidance of adaptive behavior.

It seems reasonable to presume that in a state of acute schizophrenic excitement there is, in neurophysiological terms, a heightened and relatively diffuse activity of the brain with many nerve cells firing rapidly and in a somewhat disorderly fashion, tending, thereby, to spread, or at least to maintain, a pattern of relatively random and disorganized activity.

This brings us to a reconsideration of the ideas of those brilliant pioneers, Eugen Bleuler and Hughlings Jackson. Bleuler [6] recognized that a splitting of mental activity is characteristic of schizophrenia. Jackson [7] stated that "insanities," as he called them, are due to a dissolution of the highest levels of mental integration and that such a dissolution produces negative mental symptoms through loss of the activity of these highest levels, and positive mental symptoms, such as "illusions, hallucinations, delusions, and extravagant conduct," as a result of the activities of lower levels of integration now freed from higher controls.

The present hypothesis is that what renders the highest levels of integration of the schizophrenic mind unavailable for the adaptive regulation of conduct is their preoccupation with unresolved and unresolving conflicts, and that hallucinations, delusions, and extravagant conduct are not solely a release phenomenon but reflect also the effect of disorder in the higher circuits.

Resolution of such a disorganizing conflict may be presumed to be related to the development of some effective patterning of nerve cell discharges, a patterning which, on the psychological side, relates to the developing dominance of certain ideas or patterns of action. If we regard the developing ideas as reasonable and the patterns as appropriate, we say the patient is recovering. If we regard the ideas as unreasonable and find them fixed, then, although the patient is improving in his capacity to meet the demands of daily living, we speak of a developing paranoid stabilization. Such a stabilization may perhaps be compared to the healing of an injured joint, such as a knee, with interference with flexible function by scar tissue formation.

In relation to this hypothesis, the measures of treatment utilized with schizophrenic patients may be grouped as follows:

1. Measures which seek to relieve the diffuse activity by bringing about a direct resolution of the patient's central conflict

2. Measures designed to reduce the morbid feedback of cortex to diencephalon and thereby reduce the intensity of the patient's conflict and resultant diffuse brain activity

3. Measures designed to draw the newer and higher brain structures back into the service of day-to-day adjustment

4. Measures designed to combine some of the foregoing

The resolution of conflict is a goal of psychotherapy. The resolution of conflict ordinarily depends, however, on the effective functioning of the mental apparatus. When the mental processes have already come apart in a schizophrenic split as a result of this conflict, there are, to say the least, substantial difficulties in utilizing them for the effective resolution of the conflict which has already disorganized them. Although some workers, such as Rosen, claim a good per-

centage of success by direct attack, the first method is perhaps more distinguished by its emotional appeal than by its present level of success.

For the present, it appears that direct resolution of the conflict must remain the exception, once the schizophrenic split has actually developed. On the other hand, there is every reason to believe that before the development of a schizophrenic split the wise application of psychotherapy may be an effective preventive. I stress the wise application, for it is well known that the utilization of the classical psychoanalytic approach has sometimes been blamed for precipitating a schizophrenic break. At any rate, there is considerable indication that too much uncovering therapy with too little supportive therapy may precipitate a schizophrenic disorganization in a susceptible patient. Here, as elsewhere in medicine, it is important that the therapist should be the master of his methods, not the slave of his methods. In dealing with the patient who shows tendencies toward anxious preoccupation or toward rumination, particularly if there are elements of detachment, he will do well to be sure of the reality of his emotional support of the patient before taking a risk that he may uncover too much.

If the conflict is acute, with a high level of anxiety, then it would appear that a judicious use of mild chemical sedation to reduce the anxiety from a morbid to a functional intensity may be a wise addition to psychotherapy. It is, I believe, no accident that Bowman [8] found the number of total abstainers from alcohol to be disproportionately high in the schizophrenic group. This is a statement of fact. It implies no value judgment, and I will not argue with anyone who may wish to maintain that the risk of a schizophrenic psychosis is to be preferred to the risk of an alcoholic psychosis.

If the schizophrenic development is insidious and without a high level of anxiety, there is little virtue in seeking to reduce a level of anxiety which is not high. In such a case, it is not that adaptive thinking is crowded out by an anxious preoccupation. Rather, the patient lacks motivation toward or interest in adaptive behavior adequate to compete with fantasy, and therapeutic effort must be directed primarily toward stimulating a higher level of motivation toward adjustive behavior, rather than toward the relief of anxiety.

If the defined goal must be to dampen and check the morbid resonance of cortex with diencephalon rather than to resolve it, then the most drastic, diagrammatic, and dramatic of the measures is the operation of prefrontal lobotomy. Putting a leucotome through the frontothalamic radiation certainly reduces to an important degree the extent of corticothalamic connections and should serve to dampen the hypothesized eddy of neural activity between cortex and thalamus. And, indeed, it was the response obtained which suggested the present hypothesis. The lobotomized patient appears less anxious than he was before his operation.

It is assumed that a state of conflict gives rise to the schizophrenic psychosis. Such a conflict involves the activation of two neural patterns tending toward mutually incompatible discharges. It may be assumed that these two patterns will probably involve the higher brain structures, and, particularly, the frontal lobes, to an unequal degree. Thus, in the classical conflict of sexual drive with socially determined inhibition, it is reasonable to assume that the sexual drive is less dependent upon the intactness of the frontal lobes than is the social inhibition. And we find, in fact, that frontal lobotomy tends to reduce the sexual inhibitions and, in this fashion, to reduce the sexual conflict. Prefrontal lobotomy represents, in a sense, forced reversal of the evolutionary process. The lobotomized patient is less concerned with abstractions,†, including moral principles; more stimulus-bound and stimulus-dependent; less conflicted, and, since, by all indications, less capable both of preoccupation and of a sustained conflict, certainly less capable of pre-

† Dr. Theodore Lidz has described frontal lobe deficit as essentially a limitation of associated range. Such a limitation should effectively reduce conflict.[9]

occupation with a sustained conflict. The result is a more limited, but, commonly, a more adequately functioning, personality.

The massive downward neural discharge occasioned by electroconvulsive therapy, followed as it is by a period of relative neural inactivity, particularly of the higher centers, must represent at least a transient interruption of our postulated circular thalamocortical activity. Such an interruption should increase the chances of the replacement of this activity with mental processes which serve a function of adjustment to the external world.

This treatment is in a sense analogous to the abolition of ventricular fibrillation which has been achieved by an electric shock adequate to set the entire ventricular musculature into contraction.[10] The morbid eddy of excitation is abolished thereby, and the normal cardiac rhythm reestablished itself. Similarly, in the prolonged narcosis of dauerschlaf, the activity of the cortex, in particular, is grossly depressed and the postulated circular activity must be interrupted, or at least reduced.

All of the foregoing represent direct and active intervention with therapeutic intent. The second group of therapeutic measures may be regarded by some as the more "natural" ones, for they represent an effort to encourage a recovery which in many cases appears to arise spontaneously. Success depends upon the successful recapture and utilization of the higher neural pathways for the purposes of solving problems of adaptive behavior rather than leaving them occupied with the abstracted and distorted content of schizophrenic conflict. In most cases, such a diversion can best be established by an upward extension of the patient's range of adaptive capacity. Such an upward extension can, as a rule, be brought about only gradually and presumably reflects a progressive recapture of higher neural pathways for adaptive behavior. Initially, particularly, one should not overshoot the mark. It is in general best to begin with a relatively simple and concrete level of performance.

The dynamic of effective diversion is strong motivation, and if motivation toward adaptation is sufficiently intense, adaptive activity may gradually and effectively displace schizophrenic preoccupation. This has been shown most diagrammatically in the work of Peters ‡ at the Veterans Administration Hospital, North Little Rock, Ark. Dr. Peters has begun with severely withdrawn schizophrenics who would do nothing in occupational therapy. They received subshock insulin from the medical staff to intensify their hunger and were worked with individually in graduated problem solving with food reward. Hunger plus a visible piece of food can create a strong motivation toward solving the problem of getting hold of that piece of food. These patients were not permitted to experience the frustration of failure, for their capacity to tolerate frustration and continue adaptive effort is conspicuously low. When necessary, they were given guidance toward the solution of the problem. They showed reliably greater improvement than did matched controls, either controls with subshock insulin but no problem solving or controls without either insulin or problem solving. Once the pattern of adaptive effort has been given an effective start, it may compete successfully with the schizophrenic preoccupation and disorganization. However, the extremely slow rates of development of new adaptive responses by these chronic schizophrenics were of a different order from the rate of adaptation not only by normal subjects but also by acute schizophrenic patients. It does not appear that the loss of capacity for adaptive response in the schizophrenic is irreversible, but it may become very difficult to reverse, and very slow to progress toward recovery.

The reversal of the schizophrenic process through the drawing of the newer and higher brain structures into the service of day-to-day adjustment is less diagrammatically illustrated in the usual spontaneous recovery and in the recoveries which take their origin in the development of interest, motivation,

‡ References 11 and 12.

and consequent adaptive behavior in occupational therapy, manual arts therapy, corrective therapy, music therapy, or some other area of activity therapy. Almost the whole of hospital milieu therapy relates to the same principle. The patient's adjustive responses are praised and rewarded. Concern is centered, not upon his morbid tendencies, but upon the utilization to the maximum of his capacities for normal response. That such measures meet success in many cases is well known.

As an example of a measure of treatment which tends both to check morbid resonance and to reestablish adaptive behavior, insulin coma may be cited. The injection of massive doses of insulin produces a hypoglycemia. This first dampens and then paralyzes the activity of the higher centers of the central nervous system. The most recently elaborated structures representing the highest levels of integration are the first affected and the most affected. We see a descending paralysis of activity, affecting first the cortex and then the diencephalon. We stop the process short of paralysis of the respiratory center in the medulla. Thus, we temporarily check the activity of the cortex and of the diencephalon, and when the patient recovers from coma he experiences the biological stimulus of one of the primary drives, hunger, and is strongly motivated toward the adaptive behavior of eating. Since any adaptive activity tends to promote adjustment and recovery, this combination is therapeutically useful.

Psychotherapy, as applied with psychotic patients, may, and commonly does, attack on both these fronts. Typically, successful psychotherapy begins with some reduction in anxious preoccupation. The therapist provides a measure of emotional support, of emotional security in an interpersonal relation adequate to diminish the patient's anxiety. Some therapists even utilize false assurances for this purpose, projecting themselves into the patient's psychosis and playing a role therein. Once the anxiety is at a level not overwhelming, then the work of promoting adjustment and adaptation, initially in minor ways, becomes significant. Group therapy appears particularly useful for this latter purpose. It may also have a measure of usefulness in diminishing anxiety.

The foregoing methods are useful chiefly for dealing with the disorganization which is central in schizophrenia. There are special problems related to dealing with withdrawal and dealing with paranoid stabilization.

We see withdrawal occur when interpersonal relations become too painful and too little rewarding for the person. We may see this in the autistic reaction of a young child whose relations with parental figures are more frustrating than rewarding. We see it at its height in the defensive wtihdrawal of the catatonic. Human contacts must be made rewarding, not frustrating, and the patience of Job is required. The systematic methods evolved by Roland,[13] now at the V. A. Hospital, Chillicothe, Ohio, appear to have an unusual degree of effectiveness in dealing with catatonic withdrawal. They utilize the combination of a gentle, kindly, persistent personal interest and personal stimulus with the patient encouragement of interest in constructive activity. Dealing successfully with the withdrawn catatonic patient always reminds me of the ancient fable of the contest between the North Wind and the Sun as to which could make the traveler remove his cloak.

In dealing with paranoid stabilization, it is important that we be aware of the function of paranoid projection in reducing internal tension. Degan's factor analysis[14] of Dr. Thomas Verner Moore's material reveals in the second-order factors one which ranges from depression at one extreme to paranoid projection at the other. This represents, of course, the contrast between those patients who blame themselves and those patients who blame others. Let us remember that projection serves a purpose. For one thing, it protects the patient's self-esteem. For this reason it is unlikely that we will get anywhere with the paranoid patient until his desperate need to bolster his self-esteem is reduced. And here, again, we come to that

sometimes disparaged treatment activity known as supportive therapy. The patient's need, of course, is in large part to defend himself from his own self-criticism. The sudden breakdown of a paranoid defense may result in a depressive reaction. The warm interest of another is perhaps the most significant element in enabling him to accept a greater measure of his own responsibility without thereby becoming depressed. The attack on the paranoid system must, therefore, never be a frontal attack; rather, it is a procedure of reducing need for this defense and of suggesting alternative explanations for one misinterpretation after another until the whole structure of paranoid projection is gradually weakened.

SUMMARY

In summary, the hypothesis is presented that the schizophrenic process is a progressive maladaptation resulting from a conflict which gives rise to a self-perpetuating eddy of circular activity between cortex and thalamus that amounts to a morbid resonance, and that jams the neural circuits normally serving the highest functions, leaving the direction of behavioral responses to lower levels of integration capable only of more stereotyped, inflexible, and defensive adjustments.

Conflict is regarded physiologically as the simultaneous activation of two (or more) neural patterns tending toward discharges which are mutually incompatible. Conflict with developing anxiety presumably reflects a feed-back from cortex to diencephalon. Conflict which blocks neural discharge and results in increasing tension results in increasingly diffuse neural activity which expresses itself in more diffuse thinking.

The conflict may proceed toward healthy resolution, with return to patterned neural activity and effective thinking. On the other hand, the diffuseness may progress to disorganization. Or the conflict may be somewhat reduced by a false resolution contributing toward a paranoid stabilization of the psychosis.

With this hypothesis, methods of therapy for schizophrenia may be classified in four groups. There are those direct attempts to resolve the conflict, which, unfortunately, are not often successful once the schizophrenic break has occurred. There are those methods, such as prefrontal lobotomy or electroshock, which attempt a frontal attack on the morbid resonance. There are those, such as milieu therapy, which encourage interest and motivation in constructive activities and seek, thereby, to draw the higher centers into the service of day-by-day adjustment. Two methods have been evolved in the Veterans Administration in recent years, the organized retraining of Dr. Henry Peters and the relaxation and resocialization therapy of Paul Roland. Finally, there are those methods, such as the usual psychotherapy and insulin coma, which endeavor both to reduce the morbid resonance and to increase the adaptive behavior.

The addition of Dr. Peters' methods of graduated problem solving for food reward as the patients recover from the standard treatment of insulin coma would seem very promising, particularly since the value of Peters' methods has been demonstrated on patients far less favorable for treatment than those ordinarily taken for insulin coma.

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News and Comment

GENERAL NEWS

National Institute of Mental Health Research Grants.—New research grants were awarded by the National Institute of Mental Health upon recommendation of the National Advisory Mental Health Council, November, 1954, as follows:

Anderson, John E. American Psychological Association.
Research conference on psychological aspects of aging.
One year. $9,990.

Beach, Frank A. Yale University.
Psychophysiology of reproductive behavior.
Five years. First year $14,348.

Beller, Emanuel K. Council Child Development Center.
Fear, aggression, and dependency in childhood.
Three years. First year $15,766.

Caplan, Gerald. Harvard University.
Evaluation of a mental health program for student nurses.
Two years. First year $14,430.

Coffey, Hubert S. University of California.
Relation of group tension to interpersonal role.
One year. $6,304.

Denniston, R. H. University of Wyoming.
Relation of hormonal factors to behavior.
Three years. First year $4,175.

Foote, Nelson N., and Riesman, David. University of Chicago.
Functions of play in developing adulthood.
Three years. First year $21,600.

Funkenstein, D. H. Harvard University.
Interpersonal perception in schizophrenia.
Three years. First year $9,654.

Hunt, David E. Yale University.
Effect of need for approval on children's behavior.
Two years. First year $4,390.

Jahoda, Marie. New York University.
Psychology of role acceptance in women.
One year. $10,751.

Kanfer, Frederick H. Washington University.
Studies in verbal behavior.
Three years. First year $7,208.

Overholser, Winfred. George Washington University.
Effect of psychoanalysis on therapist's techniques.
Three years. First year $15,637.

Reichard, Suzanne. Mount Zion Hospital.
Psychogenic factors in schizophrenia and the neuroses.
One year. $8,400.

Skinner, B. F., and Solomon, Harry C. Harvard University.
Experimental analysis of psychotic behavior.
Two years. First year $30,000.

Spiegel, John P., and Kluckhohn, F. R. Harvard University.
Influence of family and culture on mental health.
Two years. First year $32,011.

X-RAY TECHNICIANS SYMPOSIUM AT U.C.L.A.

Open to all registered or experienced x-ray technicians, the Second Annual X-Ray Technicians Symposium at the University of California School of Medicine at Los Angeles, sponsored by University Extension and the University Division of Postgraduate Medical Education, will be held Feb. 12 and 13.

Meeting place for the two-day gathering will be the first-floor auditorium of the new Medical Center, 13-105, at U. C. L. A., with sessions set for Saturday from 10 a. m. to 5 p. m. and Sunday from 9 : 30 a. m. to 1 : 00 p. m., according to Dr. Thomas H. Sternberg, Head of the Division.

Persons interested in attending the symposium should address Dr. Sternberg at the University of California Medical Center, Los Angeles 24, for application blanks and other information. Enrollment is limited to 140.

All subjects being presented at the symposium are result of suggestions submitted after the First Annual X-Ray Technicians Symposium. Such a plan assures the realization of the true intent in presenting these symposia, namely, to make available continuation medical education for x-ray technicians, emphasizing the fundamentals as well as the newer developments and more advanced procedures. A syllabus containing outlines or résumés of each talk will be given to each student.

The Department of Radiology of the University has extended an invitation to inspect the equipment and visit the department within the new Medical Center building. Conducted tours will circulate through the area after the Saturday afternoon and Sunday morning sessions. A certificate of completion will be given to each student upon request, according to Dr. Sternberg.

COURSE IN EMOTIONAL PROBLEMS IN OFFICE PRACTICE, U.C.L.A.

With enrollment limited to 25 persons, the University of California School of Medicine at Los Angeles, Division of Postgraduate Medical Education, announces a University Extension course in Treatment of Emotional Problems in Office Practice, scheduled to meet Feb. 10 to April 14, in the Cancer Wing of the new Medical Center of the University.

Sessions are set for Thursdays, 8 to 10 p. m. Fee for the course is $50. Applications or requests for information concerning the seminars should be made as soon as possible to Dr. Thomas H. Sternberg, University of California Medical Center, Los Angeles 24.

TRAINING IN CHILD PSYCHIATRY

Specialized training in child psychiatry is available in a number of member clinics of the American Association of Psychiatric Clinics for Children which have been approved as training centers by the Association. The training begins at a third-year, postgraduate level with minimum prerequisites of graduation from a Class A medical school, an approved general or rotating internship, and a two-year residency in psychiatry, approved by the American Board of Psychiatry and Neurology. The majority of these clinics have also been approved individually by the American Board of Psychiatry and Neurology for a third year of training and for an additional year of experience.

For further information and for application forms, write to Miss Marion A. Wagner, Administrative Assistant, American Association of Psychiatric Clinics for Children, 1790 Broadway, Room 916, New York 19.

PSYCHOANALYTICAL TRAINING FACILITIES, McGILL UNIVERSITY

Dr. W. Clifford M. Scott had been appointed Associate Professor in the Department of Psychiatry of McGill University to organize psychoanalytical training. Dr. Scott graduated from the University of Toronto in 1927. After working under the late Prof. Adolf Meyer and Prof. Macfie Campbell, he continued his studies at the National Hospital, Queen Square, and the Institute of Psychoanalysis, London. Before taking his present post he had been director of the London Clinic of Psychoanalysis and, more recently, chairman of the Board of Directors of the Institute of Psychoanalysis, teacher at the Institute of Psychiatry, and a member of the staff of the Bethlehem Royal and Maudsley Hospital, London. Associated with Dr. Scott in the establishment of psychoanalytical training at McGill University are Dr. Johann Aufreiter and Dr. Gottfriede Aufreiter, both of whom obtained their psychiatric and psychoanalytical training in Vienna.

Dr. D. Ewen Cameron, chairman of the Department of Psychiatry, in announcing this development, adds that it represents a most important addition to the training facilities offered by the Department, as it constitutes a pioneer enterprise in establishing a complete psychoanalytical

training program within the Department of Psychiatry, an enterprise which promises to be most fruitful in developing integration and interchange of knowledge between psychiatry and psychoanalysis.

Application for psychoanalytical training should be made directly to Dr. W. Clifford M. Scott, Allan Memorial Institute, McGill University, Montreal, Canada.

ASSOCIATION FOR RESEARCH IN NERVOUS AND MENTAL DISEASE

At the 34th annual meeting of the Association for Research in Nervous and Mental Disease, held in New York on Dec. 10 and 11, 1954, the following officers were elected for the year 1955:

President	Dr. J. E. Moore
First vice-president	Dr. John Romano
Second vice-president	Dr. David Seegal
Secretary-treasurer	Dr. Clarence C. Hare
Assistant secretary	Dr. Rollo J. Masselink

The subject for the 1955 meeting will be "The Neurological and Psychiatric Aspects of the Disorders of Aging." The meeting will be held on Dec. 9 and 10, 1955, in New York.

MORALITY OR IMMORALITY OF WORKS OF ART AND LITERATURE

The attitudes of the people, the community, the authorities, and the courts about the morality of works of art and literature are often not in keeping with each other because accepted standards are unknown.

A questionnaire has been developed to determine the present standards. Those who reply to this questionnaire will contribute toward the establishment of rules that may guide in the future. Questionnaire blanks and franks may be obtained from Dr. W. G. Eliasberg, 151 Central Park West, New York 23.

THE LESTER N. HOFHEIMER AWARD

The estate of Lester N. Hofheimer in May, 1947, contributed a sum of $25,000 to the American Psychiatric Association for the purpose of providing an annual award for an outstanding contribution of a research nature in the field of psychiatry or mental hygiene.

Entries for consideration of this award should be in the hands of the Hofheimer Prize Board no later than March 1, 1955. The Hofheimer Prize Board consists of eight Fellows and members of the American Psychiatric Association, of which Dr. Harold G. Wolff is chairman. Therefore, eight copies of the work to be considered should be submitted to Dr. Harold G. Wolff, at the New York Hospital, 525 E. 68th St., New York 21.

The following rules and regulations apply to such entries: "The Hofheimer Prize Board shall award each year at the annual meeting of the American Psychiatric Association a prize award to be known as the 'Hofheimer Prize' in the amount of $1,500, to a citizen of the United States or Canada, not over forty years old at the time of his publication, or submission for publication, of an outstanding contribution of a research nature in the field of psychiatry or mental hygiene. The award shall apply only to work published within a period of three years prior to the date of the award. The award may be made to each member of a group, instead of to an individual, provided that the majority of the group are citizens of the United States or Canada, and that the median age of the group did not exceed forty years at the time of publication. Such annual award of $1,500 shall be equally divided among the members of the group. Each recipient, or recipients, in the case of a group award, shall receive a certificate (the expenses of which shall be paid from the fund) indicating that the 'Hofheimer Prize' has been made possible under the terms of the Will of Lieutenant Lester N. Hofheimer, deceased. The award shall not be confined to Fellows or other members of the American Psychiatric Association. The Board may, at its discretion, omit the prize award for any one year, but the making of the award shall not be omitted for any two successive years."

RETIREMENT OF DR. ARMANDO FERRARO

Dr. Armando Ferraro, Principal Research Scientist in Neuropathology at the New York State Psychiatric Institute, retired from his position as of Nov. 30, 1954. Dr. Ferraro had served the New York State Department of Mental Hygiene without interruption in this position since Oct. 18, 1926. A farewell party was given in his honor on Nov. 24 by the employees and his colleagues on the staff of the Psychiatric Institute, who presented him with a gift of airplane luggage as a token of remembrance.

Books

The Spino-Cerebellar Degenerations. By J. G. Greenfield. A Monograph in American Lectures in Neurology. Price, 17s. 6d. Pp. 112. Blackwell Scientific Publications, 24-25 Broad St., Oxford, England; The Ryerson Press, 299 Queen St., W., Toronto 2 B, Canada, and Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1954.

J. G. Greenfield, Honorary Consultant Pathologist to the National Hospital for Diseases of the Nervous System, Queen Square, London, is one of the world's leading neuropathologists. He has written a superb monograph dealing with related degenerations of spinal cord, brain stem, and cerebellum, many of the familial forms of which sometimes have been loosely gathered together under the clinical designation of "Marie's hereditary ataxia." The term spinocerebellar degenerations as used by Greenfield in his monograph includes a group of progressive diseases characterized clinically by disturbances of the coordination of movement, or ataxia, and pathologically by degeneration of those afferent and efferant neuronal systems on which the smooth and efficient regulation of movement depends. He has utilized historical and pathological approaches in his analysis of these conditions, largely ignoring material not pathologically controlled. While the book deals mainly with hereditary disease, there is also a consideration of the idiopathic types of system degenerations of the cerebellum. The congenital dysplasias have not been included.

The book opens with an orienting chapter on anatomical and physiological considerations, followed by a section on pathogenesis and classification of the spinocerebellar degenerations. Greenfield begins the description of each disorder with a succinct historical outline, followed by a section on clinical and pathological features. When there occurs involvement of parts of the nervous system other than spinocerebellar mechanisms or of viscera, this is commented on. It may be said for those who do not know, that Greenfield is expert in general and clinical pathology, as well as neuropathology.

In this vein, there are descriptions of Friedreich's ataxia and its association with atrophy of the Charcot-Marie-Tooth type (peroneal muscular atrophy); the Roussy-Lévy syndrome (hereditary areflexic dystasia); posterior column ataxia; hereditary cerebellar ataxia, including the work of Marie, Menzel, and Holmes; olivopontocerebellar atrophy, and dentatorubral atrophy (Ramsay Hunt syndrome). Diffuse degeneration of the cerebellar cortex is the subject of one chapter; this interesting condition is associated with all sorts of noxae; among the commoner are aging, heat stroke, enteritis, syphilis, tuberculosis, alcoholism, and carcinoma. This last condition is a type of cerebellar degeneration in which there is currently no evidence of hereditary trait.

The author pays particular tribute to two neurologists for their pioneer work on the cerebellum. André Thomas gave a full description of olivopontocerebellar atrophy in his thesis of 1897 and later wrote extensively on cerebellar anatomy, physiology, and cerebellar disease. Gordon Holmes's elucidation of cerebellar function was described in his Croonian Lectures in 1922 and his Hughlings Jackson Lecture of 1939; the latter, entitled "The Cerebellum of Man," published in *Brain*, is a neurological classic. Greenfield has utilized most of the significant publications on cerebellar disease in constructing his monograph; it is particularly gratifying to note his coverage of the French literature. His thorough bibliography contains as many references to works published in other languages as in English, some indications of wide acquaintance with the subject. Numbers are appended at the end of bibliographical references to indicate the pages in the monograph on which the article in question is cited, and a three-page index covers well the material in the volume.

It is to be doubted that anyone writing in English could have produced a more scholarly discussion of a subject which up to now had been thoroughly confused by clinical speculation uncontrolled by pathological examination, to say nothing of the fact that definitive articles in foreign tongues had been largely neglected or ignored. Not only has Greenfield, from his vantage point at the National Hospital, had rather direct access to the material of such pioneers in the field as Gowers and Holmes—to say nothing of Sherrington and his school—but the unofficial Queen Square-Paris link has given him a feeling for the significant work stemming from France, heretofore generally unknown. This monograph from the pen of the *doyen* among neuropathologists will stand for a long time as the authoritative reference on the spinocerebellar degenerations. It represents yet another contribution to the unique tradition of the National Hospital, Queen Square.

Sir William Gowers 1845-1915; A Biographical Appreciation. By Macdonald Critchley. Price, 17s. 6d. Pp. 118. William Heinemann, Ltd., 99 Great Russell St., London, W.C.1, 1949.

For those who want to know or to review their knowledge about the origins and development of the National Hospital in Queen Square, London, this little book about Sir William Gowers will inform and entertain them. Concerning the hero himself, nothing particularly definitive seems to have been garnered prior to Gowers' apprenticeship to a local physician, Dr. Thomas Simpson, of Coggeshall in Essex. From that point on, Critchley outlines for us the tremendous industry and intellect of Gowers and his rapid flowering into the master who was perhaps "the greatest clinical neurologist of all times."

Gowers lived from 1845 to 1915. His adult life spanned the time when the specialty of neurology was under development. His productive life was spent in that unique institution, the National Hospital for the Relief and Cure of the Paralyzed and the Epileptic. He was but ten years the junior of his colleague, the great John Hughlings Jackson, and among his many famous associates prior to the turn of the century were Radcliffe, Reynolds, Buzzard, Bastian, Beevor, Ferrier, Horsley, Gunn, Tooth, Ballance, Taylor, Bradford, and Russell.

Besides his talents as a great physician, teacher, and original observer, Gowers is particularly remembered for his amazing survey of the then new specialty, with his many writings. Like others of his Queen Square colleagues, he had highly developed the art of facile expression. His was an abiding concern with the proper uses of language, and he was constantly alert to say exactly what he meant and to say it beautifully and with charm. His many monographs remain the keystone of neurological literature in English-speaking countries. His magnum opus was the great "bible of neurology," in two volumes, entitled, "Manual of Diseases of the Nervous System." It is still a Queen Square tradition that "anyone who thinks he has stumbled upon something new or obscure should not neglect to search Gowers' 'Manual' before claiming originality." Surely even today none who fancy themselves neurologists should neglect Gowers' "Manual," despite the plethora of textbooks that have followed.

Critchley's biography of Gowers is short; it can be read in an evening. The little book is printed on nonreflective paper; there are 11 illustrations and an index of 4 pages. A bibliography of Gowers' published works, extending from the year 1872 through 1910, occupies 18 pages. Some of his studies are recorded in shorthand script, at which he was adept, and have not yet been transcribed.

Critchley, who was formerly the Dean of the National Hospital faculty and remains one of its Senior Physicians, has written entertainingly about Gowers, that "apogee of the great physician." At the same time he has recreated in these pages some of the grand neurological tradition of the institution known to many as Queen Square.

Malformations et tumeurs vasculaires du cerveau. By Roger Pluvinage. Price, 3,000 francs. Pp. 323. Masson & Cie, 120 Boulevard Saint-Germain, Paris 6, 1954.

This monograph is an attempt to show the practical importance of malformations and vascular tumors of the brain. It is not intended to be a complete study of the question but attempts principally to give a summary of such problems as seem apparent at the present time. Therefore, the cases on which the study rests are given very briefly, and only to illustrate certain points. Most of the material comes from the clinic of the late Prof. Clovis Vincent, but many cases have been accumulated later.

The book begins with a discussion of intracranial aneurysms; it follows lines of thought that are fairly acceptable. The second half deals with cerebral angiomas. The classification given is one that is now generally accepted—arterial angiomas, cerebral angiomas, Sturge-Weber syndrome, cavernous angiomas, and hemangiomas of the Lindau type—and ends with the general nosological study of these tumors and malformations. There is an abundant bibliography, divided according to the different sections, and the book has an index of subjects, as well as authors. The book is very well printed on good paper, and the illustrations are clear and pertinent to the text. This work is a very useful summary of the present situation of the subject and can be highly recommended to neurologists and nuerosurgeons.

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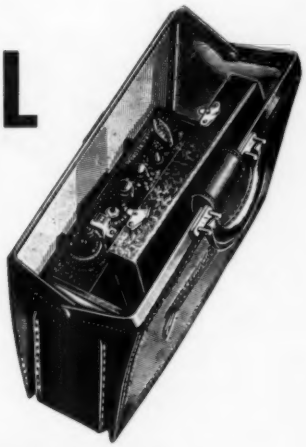

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